

Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy

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Loss of insight is one of the core features of frontal/behavioural variant frontotemporal dementia (FTD). FTD shares many clinical and pathological features with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). The aim of this study was to investigate awareness of cognitive deficits in FTD, CBD and PSP using a multidimensional approach to assessment, which examines metacognitive knowledge of the disorders, online monitoring of errors (emergent awareness) and ability to accurately predict performance on future tasks (anticipatory awareness). Thirty-five patients (14 FTD, 11 CBD and 10 PSP) and 20 controls were recruited. Results indicated that loss of insight was a feature of each of the three patient groups. FTD patients were most impaired on online monitoring of errors compared to the other two patient groups. Linear regression analysis demonstrated that different patterns of neuropsychological performance and behavioural rating scores predicted insight deficits across the three putative awareness categories. Furthermore, higher levels of depression were associated with poor anticipatory awareness, reduced empathy was related to impaired metacognitive awareness and impaired recognition of emotional expression in faces was associated with both metacognitive and anticipatory awareness deficits. The results are discussed in terms of neurocognitive models of awareness and different patterns of neurobiological decline in the separate patient groups.

Keywords: loss of insight; frontotemporal dementia; progressive supranuclear palsy; corticobasal degeneration; neuropsychological deficits

Abbreviations: ACC = anterior cingulate cortex; AD = Alzheimer’s disease; CBD = corticobasal degeneration; CFQ = cognitive failures questionnaire; DLPFC = dorsolateral prefrontal cortices; FAB = frontal assessment battery; FrSBe = Frontal Systems Behavioural Scale; FTD = fronto-temporal dementia; NAT = naturalistic action task; PSP = progressive supranuclear palsy; SART = sustained attention to response task; SO = significant other

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Introduction

Early loss of insight, or the inability to accurately perceive changes in behaviour and personality, is one of the core clinical features of frontal variant frontotemporal dementia (fvFTD) (Neary *et al.*, 1998). Systematic studies of the degree and nature of loss of insight in frontotemporal dementia (FTD) are rare however, and clinically, loss of insight is most often only assessed using clinical interviews rather than using validated quantitative measures (Diehl and Kurz, 2002; Rankin *et al.*, 2005). In two studies that have explicitly investigated loss of insight in FTD, both

found that FTD patients were significantly more impaired than patients with Alzheimer’s disease at identifying personality changes since their illness (Rankin *et al.*, 2005) and self-monitoring their memory performances (Souchay *et al.*, 2003).

Lack of insight has been demonstrated to cause increased stress and caregiver burden (Seltzer *et al.*, 1997) and can result in poor patient–caregiver interaction (Hutchinson *et al.*, 1997). Poor compliance with medication and performing dangerous or difficult activities have also been

associated with loss of insight (McGlynn and Schacter, 1989; Cotrell and Wild, 1999). A proportion of patients with AD also show loss of insight or anosognosia. The clinical relevance for investigating loss of insight becomes apparent when one considers that in AD, preserved insight is associated with better treatment outcome (Ryan *et al.*, 2006).

Frontotemporal dementia shares many clinical, radiological and pathological features with the atypical sporadic parkinsonian movement disorders known as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Kitagaki *et al.*, 2000; Cordato *et al.*, 2005). All three disorders may exhibit atrophy of the frontal and/or temporal lobes. Furthermore, at the molecular level, many cases of FTD (especially familial cases) and all cases of both CBD and PSP are related to abnormal function/levels of the microtubule associated protein tau. For CBD, most diagnostic criteria define a movement disorder, including rigidity, apraxia, cortical sensory loss or alien limb (Lang *et al.*, 1994; Litvan *et al.*, 2003). However, it has been noted that many patients with CBD develop or present with a frontal dementia or features of a progressive non-fluent aphasia, indicating CBD is a cognitive disorder as well as a motor disorder, making this condition difficult to distinguish from other neurodegenerative disorders such as FTD, PSP and AD (Litvan *et al.*, 1997; Frattali *et al.*, 2000; Kertesz *et al.*, 2000; Lang, 2000; Mathuranath *et al.*, 2000; Graham *et al.*, 2003; Bak *et al.*, 2005). PSP is another commonly misdiagnosed neurodegenerative akinetic rigid disorder which can present with axial rigidity, vertical gaze palsy and recurrent falls. Neurocognitive deficits can also be a feature of PSP, and executive function deficits, including set-shifting, planning and categorization are a frequent feature of PSP (Grafman *et al.*, 1995; Litvan *et al.*, 1996; Soliveri *et al.*, 1999; Litvan *et al.*, 2003; Boeve *et al.*, 2003; Bak *et al.*, 2005). Misdiagnosis of both CBD and PSP with Parkinson disease is common (Litvan *et al.*, 2003). Recent evidence indicates that patients with Parkinson disease can demonstrate impaired self-awareness in multiple domains, based on discrepancy between patients and their caregivers (Seltzer *et al.*, 2001; Leritz *et al.*, 2004). No studies have examined loss of insight specifically in CBD and PSP.

The Dissociable Interactions and Conscious Experience (Soliveri *et al.*, 1999) Model (McGlynn and Schacter, 1989; Schacter, 1990) and its later development to the Conscious Awareness Model (CAM) (Litvan *et al.*, 1996, 1997; Agnew and Morris, 1998; Litvan *et al.*, 2003; Ryan *et al.*, 2006) propose neurocognitive models of awareness. The CAM was developed to explain awareness deficits in Alzheimer’s disease, and so may be useful to help explain loss of insight in other neurodegenerative disorders, such as FTD, CBD and PSP. This model includes a comparator system within the central executive to monitor mismatches between a personal database and experiencing cognitive failures and successes. When a mismatch is detected, a signal is sent to

the metacognitive awareness system which leads to conscious experience of failure. If the executive system is not functioning correctly, the comparator mechanism may not pick up mismatches, and so failures in cognitive performance may not reach metacognitive output or conscious awareness. This is referred to as ‘executive anosognosia’ in the CAM.

Consistent with this type of model, studies examining lack of insight and deficits in self-awareness in AD have shown associations with impaired insight and dysexecutive symptoms (Weinstein *et al.*, 1992; Dalla Barba *et al.*, 1995; Souchay *et al.*, 2003). A relationship between impaired self-monitoring on a memory task and executive function deficits was also found in one study with patients with FTD (Souchay *et al.*, 2003). Other studies have shown that tasks of frontal function predicted anosognosia in Alzheimer’s disease (Lopez *et al.*, 1994). Further investigations with patients with Alzheimer’s disease showed that anosognosia correlated with hypoperfusion of the right dorsolateral frontal lobe (Starkstein *et al.*, 1992; Reed *et al.*, 1993). McDaniel *et al.* (1995) suggested that spread of pathology to the frontal cortex resulted in more impaired insight.

A number of recent neuroimaging studies have implicated various aspects of self-awareness with the frontal lobes (Vogelely *et al.*, 2001; Fossati *et al.*, 2003; Phan *et al.*, 2004; Boxer *et al.*, 2006) and have also implicated parietal structures (Vogelely *et al.*, 2001). Abu-Akel (2003) differentiated mentalizing about oneself into three modules, relating to three different neuroanatomical areas. He argues that parietal structures are where information about oneself is initially represented, followed by evaluation in the limbic–paralimbic module for personal relevance and meaning, and finally the information about oneself undergoes executive processes in the prefrontal module, including error monitoring, planning, inhibition of responses, similar to Morris and Hannesdottir’s ‘executive anosognosia’ proposal (Ryan *et al.*, 2006). Rankin *et al.* (2005) propose that according to the Abu-Akel model, FTD patients have more damage to prefrontal regions of this third module which is involved in the processing of information about oneself.

Researchers have called for more ‘quantitative operationalization of this core criterion’ in FTD patients to improve characterization of this symptom and the disease as a whole (Rankin *et al.*, 2005). More complete and systematic studies of impaired awareness in atypical and subcortical dementias have also been called for (Leritz *et al.*, 2004; Aalten *et al.*, 2005). Clinically based models of self-awareness have been developed to understand different facets of insight and to guide rehabilitation. Crosson and colleagues (Crosson *et al.*, 1989; Barco *et al.*, 1991) divided awareness into ‘intellectual awareness’, which represents a patient’s ability to recognize his/her deficits or impaired functioning, ‘emergent awareness’, which represents a patient’s ability to detect their difficulties as they emerge, and ‘anticipatory awareness’, which represents a patient’s

ability to predict when difficulties will arise because of their deficits. The hierarchical structure of this model has been criticized (Toglia and Kirk, 2000; Abreu *et al.*, 2001), and more interactional models have differentiated between ‘metacognitive’ knowledge or declarative knowledge about one’s abilities, which would incorporate elements of intellectual awareness, and ‘online monitoring’ of performance during tasks, which relates to emergent awareness and anticipatory awareness (Toglia and Kirk, 2000).

Measuring these different facets of awareness calls for several different approaches. ‘Metacognitive awareness’ is assessed by comparing self-ratings to significant other or clinician ratings, such as the Patient Competency Rating Scale (PCRS) (Prigatano and Fordyce, 1986; Fleming *et al.*, 1996; Sherer *et al.*, 1998), interviews (Fleming *et al.*, 1996; Ownsworth *et al.*, 2006) and comparison of patients’ reports to neuropsychological performance (Anderson and Tranel, 1989; Allen and Ruff, 1990). To assess ‘anticipatory awareness’ comparisons is made between patients’ predictions of performance and actual performance (Fischer *et al.*, 2004). More recently, evaluation of ‘emergent awareness’ has been gauged by online monitoring of errors (O’Keefe *et al.*, 2004; McAvinue *et al.*, 2005). Applying different indices to assess the multifaceted aspects of awareness deficits represents an important step forward (Fleming *et al.*, 1996; Fischer *et al.*, 2004). Markova and Berrios (2001) propose that an important methodological advantage of using diverse measures is that different ‘objects of insight’ are assessed; this is not only important for generalizing from assessment of a single specific ‘object of insight’ (Ownsworth *et al.*, 2006), but also for taking into account the generalized pathology affecting the frontal lobes in different patient groups. Frontosubcortical pathways will be differentially affected due to variable patterns of atrophy and neurotransmitter disruption that, in turn, will disrupt different domains of functioning from social and emotional function to motor, attention and executive control processes. A complete multidimensional approach to assessment of awareness can inform theoretical models, develop clinical methods of assessment, develop tasks suitable for neuroimaging studies of self-reflection and awareness, and guide rehabilitation of this complex phenomenon (Prigatano and Fordyce, 1986; Toglia and Kirk, 2000; Fischer *et al.*, 2004; Sherer *et al.*, 2005; Ownsworth *et al.*, 2006).

The present study is the first systematic and quantitative examination of insight deficits in FTD, CBD and PSP in relation to neuropsychological performance. The goal of this study was to examine awareness of deficit impairment across patient groups with FTD, CBD and PSP and controls with a multidimensional approach using the models of awareness proposed by Toglia and Kirk (2000) and Crosson and colleagues (Crosson *et al.*, 1989; Toglia and Kirk, 2000) as a guiding framework. Insight was assessed on three levels: metacognitive knowledge, online emergent awareness and online anticipatory awareness.

Material and methods

Eligible participants who agreed to participate gave informed consent according to the Declaration of Helsinki, the Mater Misericordiae Hospital Ethics Committee and Trinity College Dublin Ethics Committee.

Participants

Fifty-five participants took part in this study. This included 35 patients and 20 neurologically healthy controls.

Patients ($n = 35$)

The patients were recruited from academic hospitals in the Republic of Ireland from June 2003 to March 2005. The referred patients were then screened for core criteria for the disorders (FTD, PSP and CBD) by the neurologist at a dementia and movement disorders clinic. Exclusion criteria included previous head trauma, a history of major psychiatric disorder, evidence of previous or concurrent neurological condition such as stroke or epilepsy, use of neuroleptic agents or history of drug or alcohol abuse. The clinical diagnosis of FTD was assigned using the current consensus criteria as first proposed by the Lund and Manchester Groups (Brun *et al.*, 1994). This indicates a clinical syndrome and not a pathological one as the term frontotemporal lobar degeneration (FTLD) implies (McKhann *et al.*, 2001). As such, semantic dementia, primary progressive aphasia (PPA) and fvFTD are all encompassed within the term FTD, consistent with both Brun *et al.* (1994) and McKhann *et al.* (2001). Clinical diagnosis of PSP was assigned according to the consensus clinical criteria as first published by Litvan *et al.* (1996), the modified version of this original set of criteria as suggested by a Scientific Issues Committee (SIC) taskforce in 1993 that distinguishes clinically possible, clinically probable and clinically definite disease (Litvan *et al.*, 2003). Clinical diagnosis of CBD was assigned according to the suggested clinical research criteria from the SIC taskforce (Litvan *et al.*, 2003). Using these criteria 14 FTD, 11 CBD and 10 PSP were defined. Of the 14 cases assigned the clinical diagnosis of FTD, 11 were frontal (behavioural) variant FTD from clinical onset, 1 was the PPA subtype at onset (pure word finding deficits in first 2 years) with subsequent involvement of other frontal dysexecutive features, 1 was semantic dementia (with prominent new disinhibition at time of testing) and 1 case was motor neuron disease with FTD (impaired lexical fluency with attentional deficit). Disease duration was assessed based on time since the first symptoms were reported by significant others/carer.

Controls ($n = 20$)

The control groups consisted of caregivers of the patient participants. The caregiver group consisted of 20 neurologically healthy adults, 16 of who were spouses/partners of the recruited patients and 4 of who were caregiver children of patients.

Materials and procedure

The clinical neurological examination (2 h) was conducted by a clinical neurologist and neuropsychological assessment was examined by the research psychologist (2.5 h) and included all awareness measures. All participants were given rest sessions at regular intervals and upon request during both sessions. Testing took place in a clinical research room in the Mater Misericordiae University Hospital or in the home of the patient. It was ensured that all patients were able to understand and

perform brief practice trials before administration of the key neuropsychological measures.

Screening tests

A number of short screening tests for cognitive functioning were administered throughout both the sessions. These included:

National Adult Reading Test (NART) (Nelson, 1982; Nelson and Willison, 1991) as an estimate of premorbid intellect. *Mini-Mental State Examination (MMSE)* (Folstein *et al.*, 1975) as a measure of general cognitive function.

Hospital Anxiety and Depression Scale (HADS), an indication of anxiety and depression levels (Zigmond and Snaith, 1983).

Neuropsychological measures

Each participant underwent a comprehensive neuropsychological examination that included the following tests.

Memory

Subtests from the ‘Wechsler Memory Scale (WMS 111)’ (Wechsler *et al.*, 1998) included: Immediate and Delayed Story Recall (Logical Memory 1 and 11), Immediate and Delayed Face Recognition (Faces 1 and 11), Digit Span (Forward and Backward), Spatial Span (Forward and Backward).

Attention and executive function tasks

Sustained Attention to Response Task (SART) (Robertson *et al.*, 1997)

The Fixed SART consisted of digits from 1 to 9 being presented in a fixed order from 1 to 9 for 25 presentations of this sequence. Participants are required to respond by a mouse-click to every go-target and withhold response for the rare no-go target (the number ‘3’). The no-go target was presented 25 times. In this study, a modified version of the fixed SART was administered to allow for slower processing of information by the patients. Presentation of the targets and masks were slowed by 50% compared to previous studies. Three blocks of the fixed SART were run.

Trail making test (Reitan, 1958) psychomotor processing speed (part A) and mental flexibility component (part B).

Verbal fluency—FAS test (Benton and Hamsher, 1976; Spreen and Strauss, 1998)

*Frontal assessment battery (Dubois *et al.*, 2000)*

*XY Response Inhibition Task (Garavan *et al.*, 1999, 2002)*

A modified version of the XY response inhibition task described in Garavan *et al.* (2002) was run. In this task, participants were required to respond with a mouse-click to the letters X and Y. The letters X and Y are presented in a series of an alternating pattern (X, Y, X, Y, X, Y, ...). Participants were required to intermittently inhibit their responses when the alternating sequence was interrupted, that is when two Xs or two Ys were presented in succession. (X, Y, X, Y, X, X, ...). There were 40 lures (no-go target) and 590 go-targets.

‘Visuospatial Orientation Subtest from Visual Object and Space Perception Battery’ (VOSP) (Warrington, 1991): the VOSP Position Discrimination Test. This is a forced-choice procedure, where participants are required to select which of the two dots presented are exactly in the centre of the square in the testing materials provided.

Everyday actions

‘Naturalistic Actions Test’ (NAT) (Levine *et al.*, 2000): The NAT is a performance-based test to measure how well participants

perform naturalistic action, learned sequential, object-oriented behaviour in the pursuit of everyday goals. The Task 3 subtest was used in this study (packing a lunchbox and a schoolbag).

Emotional processing

‘Facial Emotion Processing’ (Ekman and Friesen, 1976; Best *et al.*, 2002): Participants were presented with 60 black-and-white photographs (Ekman’s Faces) of men and women expressing happiness, surprise, fear, disgust, anger and sadness. Photographs were presented for 5 s each and participants were asked to choose the label that best described the expression, as in (Best *et al.*, 2002).

Self and significant other (SO) questionnaire ratings

Each patient completed the following scales during testing sessions, as did a SO regarding each patient’s behaviour. For controls, a reliable informant also filled in a SO rating regarding the controls’ competency (usually a neurologically healthy sibling, friend or child). Therefore, each participant (both patients and controls) had a self-rated and SO-rated questionnaire from the three questionnaires, the PCRS (Prigatano and Fordyce, 1986), the Frontal Systems Behavioural Scale (FrSBe) (Grace and Malloy, 2002) and Cognitive Failures Questionnaire (CFQ) (Broadbent *et al.*, 1982). The Measure of Empathic Tendency (MET) (Mehrabian and Epstein, 1972) was also administered to each participant but was not rated by a SO.

Awareness measures

Metacognitive knowledge

(1) Awareness Interview—Adapted (Anderson and Tranel, 1989).

The interview schedule and scoring is described in Anderson and Tranel (1989). There were 10 domains assessed by the Awareness Interview: Diagnosis, Motor Functioning, Thinking, Orientation, Memory, Attention, Language, Visual Perception, Activities of Daily Living and Overall Performance and Ability to Return to Work. The Awareness Index ranged from 0 (representing no discrepancy between participant’s self-report and neuropsychological performance) to 20 (representing maximum discrepancy).

(2) Discrepancy Scores on Questionnaires Self and Other (Prigatano and Fordyce, 1986; Grace and Malloy, 2002).

Of the questionnaires that were administered, three were given to both the participants and a SO to rate. These were the PCRS (Prigatano and Fordyce, 1986), the FrSBe (Grace and Malloy, 2002) and the CFQ (Broadbent *et al.*, 1982). These three questionnaires were rated for identical items by participants and a SO. The discrepancy score was derived by subtracting the SO-rated score from the self-rated score; therefore, a negative score suggests the participant has reduced knowledge of their deficit compared to a SO, whereas, a positive score suggested the participant has increased knowledge of their deficit than the SO.

Online emergent awareness

(3) Error-monitoring on the SART (McAvinue *et al.*, in press; O’Keeffe *et al.*, 2004).

As participants performed the three blocks of the SART, error awareness was measured by asking participants to verbally indicate their awareness of making an error by saying the word ‘hit’ following an error of commission on the no-go

target (the number '3'). The proportion of aware errors over the total number of errors made gave the overall error awareness score on the SART.

(4) Error-monitoring on XY.

Participants were asked to verbally indicate their awareness of their errors by saying, 'hit' following an error of commission (failing to inhibit their response on the no-go target). The proportion of aware errors over the total number of errors made gave the overall error awareness score on the XY task.

Online anticipatory awareness

(5) Prediction tasks—discrepancy between predicted and actual performance in cognitive tasks (Fischer *et al.*, 2004; Marcel *et al.*, 2004).

Accuracy of prediction on cognitive tasks was assessed using WMS Digit Span (Forwards and Backwards), WMS Spatial Span (Forwards and Backwards) and Verbal Fluency (Fassbender *et al.*). Participants were asked prior to performing each of these tasks to predict how many numbers they would remember (Digit Span), or patterns they would remember (Spatial Span) or words they could come up with in 1 min beginning with a certain letter (Verbal Fluency). Prediction accuracy was assessed in each task by calculating an average score [(prediction – performance)/prediction × 100].

Results

Demographic and screening data

Groups were well matched in terms of sex [$\chi^2 = 5.495$, $df = 3$, $P > 0.05$], education level [$F(3,49) = 0.625$, $P > 0.05$], estimated pre-morbid IQ [$F(3,44) = 1.713$, $P > 0.05$], HADS anxiety [$F(3,48) = 1.831$, $P > 0.05$], HADS depression [$F(3,48) = 0.353$, $P > 0.05$]. The three patient groups did not differ significantly in terms of disease duration (time since first symptoms reported by SO) [$F(2,31) = 0.519$,

$P > 0.05$]. There was a significant effect for participant age [$F(3,50) = 4.118$, $P < 0.05$]. *Post hoc* bonferroni comparisons indicated that PSP participants were significantly older than control participants ($P < 0.05$). No other groups differed significantly in terms of age. There was a significant effect for MMSE scores [$F(3,50) = 0.519$, $P < 0.05$]. *Post hoc* bonferroni comparisons indicated that FTD patients had significantly lower MMSE scores than both PSP patients ($P < 0.05$) and controls ($P < 0.01$).

Patient and control performance on neuropsychological tests

One-way between-groups Analysis of Variance revealed a number of significant between-group differences. Table 1 displays the mean scores and standard deviations for each group on each neuropsychological test. ANOVA *F*-values and significance level are also displayed, as are *post hoc* bonferroni comparisons, indicating where the specific group differences lie. Only Trail Making Test, SART and XY Response Inhibition Task did not show significant effect of group, although a trend towards significance was evident for group on the SART ($P = 0.06$).

Macro-level analysis of composite awareness scores

Composite scores for Metacognitive Knowledge (awareness index, PCRS discrepancy score, FrSBe discrepancy score and CFQ discrepancy score), Online Emergent Awareness (overall error awareness on fixed SART and XY task) and Online Anticipatory Awareness (overall prediction tasks accuracy, digit span, spatial span and verbal fluency) were calculated based on *z*-scores from each of the individual awareness measures. Analysis of the composite

Table 1 Neuropsychological test scores for each participant group

Cognitive functions	Neurocognitive tests	FTD	CBD	PSP	Caregivers	<i>F</i> value	<i>P</i> value
Memory mean (SD)	WMS Logical Memory I	19.0 (12.9) ^a	23.09 (8.8) ^b	29.2 (6.5)	34.45 (9.6) ^{a,b}	7.446	<0.001
	WMS Logical Memory II	7.38 (8.1) ^a	12.27 (8.7) ^b	15.8 (5.4)	20.15 (7.6) ^{a,b}	7.818	<0.001
	WMS Faces I	28.57 (5.7) ^a	29.91 (6.4)	28.8 (3.9) ^c	35.35 (5.5) ^{a,c}	5.642	<0.01
	WMS Faces II	28.86 (4.5) ^a	29.64 (4.7) ^b	29.1 (4.7) ^c	35.6 (4.7) ^{a,b,c}	8.027	<0.001
	WMS Digit Span	13.67 (6.0) ^a	15.55 (5.2)	15.5 (3.4)	18.5 (3.3) ^a	3.23	<0.05
	WMS Spatial Span	9.31 (3.1)	8.55 (5.2) ^b	10.6 (5.1)	13.35 (4.1) ^b	3.883	<0.05
Attention mean (SD)	TMT-difference B–A (s)	119.35 (77.3)	149.52 (82.8)	144.94 (98.6)	79.07 (76.7)	1.956	>0.05
	SART (mean errors of commission)	6.185 (4.4)	4.542 (3.0)	2.815 (2.4)	3.316 (2.2)	2.585	>0.05
Executive functions mean (SD)	XY task (errors of commission)	20.56 (10.0)	15.63 (8.9)	18.44 (8.9)	14.3 (9.3)	1.099	>0.05
	Verbal fluency FAS (total)	25.43 (19.9) ^a	20.09 (9.3) ^b	27.11 (15.8) ^c	47.75 (14.8) ^{a,b,c}	9.976	<0.001
	Frontal assessment battery	11.43 (5.3) ^a	9.09 (5.0) ^b	12.22 (3.5) ^c	16.60 (1.6) ^{a,b,c}	10.132	<0.001
Visuospatial mean (SD)	VOSP dot discrimination	19.0 (1.2)	17.55 (3.2) ^b	17.2 (2.9) ^c	19.8 (0.5) ^{b,c}	5.105	<0.01
Real-life functions mean (SD)	Recognition of facial emotions (% Acc.)	61.53 (23.8) ^a	57.88 (18.9) ^b	59.67 (17.9) ^c	78.99 (9.4) ^{a,b,c}	5.252	<0.01
	Naturalistic actions task	1.69 (2.3) ^a	2.11 (1.9) ^b	2.22 (1.9) ^c	4.35 (1.2) ^{a,b,c}	6.491	<0.01

Post hoc comparisons between each group are indicated by the following symbols:

^a*Post hoc* comparisons ($P < 0.05$): controls vs patients with FTD. ^b*Post hoc* comparisons ($P < 0.05$): controls vs patients with CBD.

^c*Post hoc* comparisons ($P < 0.05$): controls vs patients with PSP.

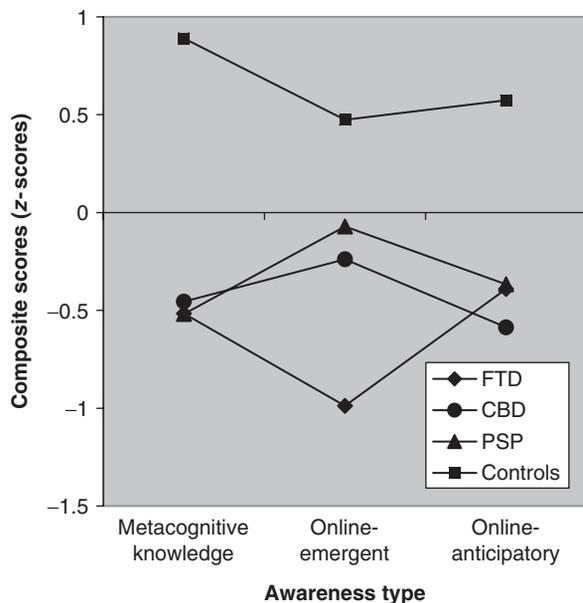


Fig. 1 Composite scores for Metacognitive Knowledge, Online Emergent Awareness and Online Anticipatory Awareness (calculated based on z-scores from each of the individual awareness measures) as a function of Group.

scores represents a macro-level analysis of the data. In order to investigate performance across the different awareness measures, a mixed ANOVA was conducted. The between-subjects factor was ‘Group’ (four levels: FTD, CBD, PSP and Controls) and the within-subjects factor was ‘Awareness Type’ (three levels: Metacognitive Knowledge, Online Emergent Awareness and Online Anticipatory Awareness). To control for actual number of errors committed during emergent awareness a ‘Total Errors’ (combining XY and SART errors) was added as a covariate to the ANOVA model. ‘Total Errors’ did not interact with ‘Awareness Type’ ($F < 1$). However, there was a significant main effect of ‘Group’ [$F(1,39) = 13.74$, $P < 0.001$]. Irrespective of awareness type, all patient groups had a poorer awareness score than controls (all $P < 0.05$). The main effect for ‘Awareness Type’ [$F(2,78) = 1.28$, $P > 0.05$] did not reach significance. An interaction effect between ‘Group’ and ‘Awareness Type’ was significant [$F(6,78) = 2.26$, $P < 0.05$]. This interaction was driven by the fact that FTD patients were significantly worse on Online Emergent Composite scores than both CBD patients [$t(15) = -2.200$, $P < 0.05$] and PSP patients [$t(15) = -3.097$, $P < 0.01$]. *Post hoc t* tests also revealed that FTD patients were significantly worse on Online Emergent than Metacognitive Knowledge [$t(7) = 5.391$, $P < 0.001$] and than Online Anticipatory [$t(6) = -4.290$, $P < 0.01$]. Controls scored significantly lower on Online Emergent compared to Metacognitive Knowledge also [$t(19) = 3.242$, $P < 0.01$]. No other significant differences were evident for within-subject factors. Figure 1 depicts this interaction.

Does self-awareness differ according to domain of insight?

The aforementioned analysis demonstrates that patients do not differ from each other with respect to metacognitive knowledge of their deficits; however, if different neural networks are engaged depending on awareness within specific cognitive, perceptual and motor domains, it is conceivable that patients will show differential impairments depending on the object of insight. Alternatively, if the neural mechanisms of awareness are common to all functional systems, then awareness deficits should be of equal severity across each object of insight and for all patient groups.

A varimax rotation Principal Components Analysis (PCA) was performed on the awareness index scores across all the different subscales that reflect different objects of insight that an individual can be aware of; these include: motor, thinking, orientation, memory, attention, language and visual perception. PCA was conducted to see if there were linear combinations across these awareness domains that represent separate dimensions within the data. Four components were extracted with eigenvalues > 1 : this model accounted for 85.5% of the total variance for the awareness index scores. The rotated component matrix showed that the first factor was associated with speech and thinking (Eigenvalue = 1.9, % of variance = 27.7); the second factor represented motor and perceptual awareness (Eigenvalue = 1.7, % of variance = 24.7); the third factor accounted for awareness in the attention and memory domains (Eigenvalue = 1.3, % of variance = 18.6) and the fourth factor was associated with awareness of orientation (Eigenvalue = 1.0, % of variance = 14.5).

Following reduction of the data into four orthogonal components, analysis of variance was carried out to test whether the extracted factor scores differ across the patients groups. A mixed factorial ANOVA was conducted with Group (FTD, CBD and PSP) as the between-subjects factor and Component (factors 1–4) as the within-subjects factor. There was no main effect of Group ($F < 1$) or Component ($F < 1$) and no Group \times Component [$F(6,63) = 2.08$, $P > 0.05$] interaction suggesting that the observed awareness deficits did not differ as a function of the domain of awareness. Therefore, the results suggest that, irrespective of the object or mental contents of awareness, a general impairment of awareness is pervasive across all the three patient groups.

What is the relationship of awareness composite scores to neuropsychological and rating scores for patient participants?

We adopted the automatic selection procedure (backward stepwise regression) in which the neuropsychological/rating variables were entered into the equation that encompassed a full range of potential cognitive-deficit areas for all patients; these included: everyday cognitive failures and actions slips,

Table 2 Pearson product-moment correlations between awareness category and linear regression predictors across all patients

	Metacognitive knowledge	Online-emergent awareness	Online-anticipatory awareness
Linear regression predictors			
FrSBe total (other-rated)	−0.765**		
NAT	0.556**		
Total FAS words	0.594**		
SART errors		−0.439*	
FAB			0.706**
FrSBe total (other-rated)			−0.548**
XY response inhibition errors			−0.442*
CFQ-other			−0.295

*Significant at $P < 0.05$; **significant at $P < 0.01$.

FAB = Frontal Assessment Battery; CFQ = Cognitive Failures Questionnaire; FAS = F, A, S Verbal Fluency Test; FrSBe = Frontal Systems Behavioural Scale; NAT = Naturalistic Actions Task; SART = Sustained Attention to Response Task; XY = response inhibition task in which subjects inhibit response to a repeated stimuli.

executive control failures, behavioural and social dysfunction, inattention and disinhibition and memory dysfunction.

Variable predictors for metacognitive awareness

Backward stepwise regression produced a significant model [R^2 change = -0.018 , $F(5,34) = 19.81$, $P < 0.0001$] after five iterative steps in which variables were rejected. The remaining variables which did not meet the exclusion criteria were the FrSBe (other rating) [β (standardized regression coefficient) = -0.631 , $P < 0.0001$], the Naturalistic Action Task (NAT) score [$\beta = 0.266$, $P = 0.016$], the Frontal Assessment Battery (FAB) score [$\beta = 0.296$, $P = 0.032$] and SART errors [$\beta = -0.170$, $P = 0.09$]. All variables were entered for linear regression (with the exception of SART errors which did not reach the 0.05 criteria for significance) and a significant model was observed [R^2 change = 0.79 , $F(4,27) = 21.57$, $P < 0.0001$] in which the FrSBe-other ($P < 0.0001$) and NAT score ($P = 0.016$) were significant predictors of metacognitive awareness. The FAB did not reach significance ($P = 0.103$).

Variable predictors for emergent awareness

The backward stepwise regression procedure produced a significant model after nine iterative steps [$R^2 = -0.064$, $F(1,34) = 7.3$, $P = 0.011$]. All variables were rejected bar one: SART errors [$\beta = -0.426$, $P = 0.011$]. Therefore, sustained attention impairment was solely predictive of emergent awareness performance.

Variable predictors for anticipatory awareness

After six iterative steps the backward stepwise procedure yielded a significant model [R^2 change = -0.005 , $F(4,34) = 14.03$, $P < 0.0001$]. The following variables were selected: CFQ-other [$\beta = 0.703$, $P = 0.001$], FrSBe-other

[$\beta = -0.791$, $P < 0.0001$], FAB [$\beta = 0.389$, $P = 0.004$] and XY errors [$\beta = -0.416$, $P = 0.002$]. All the abovementioned variables were significant predictors for anticipatory awareness. Table 2 displays the Pearson Product-Moment Correlations Between Awareness Category and Linear Regression predictors across all Patients.

What is the relationship of awareness composite scores to emotional processing of the patients?

Poor ability to recognize expressed emotion in the Ekman faces was highly correlated with impaired Metacognitive ($r = 0.591$, $P < 0.0001$) and anticipatory awareness ($r = 0.789$, $P < 0.0001$). Separately, low empathy as recorded by the MET was associated with a deficit of metacognitive awareness ($r = -0.383$, $P = 0.04$) and higher levels of depression reported on the HAD scale was associated with impaired anticipatory awareness ($r = -0.457$, $P = 0.014$). Emergent awareness did not correlate with any measure of emotional functioning.

Discussion

This is the first comparative study to investigate loss of insight in FTD, CBD and PSP. Insight was examined in the context of an interacting model (Toglia and Kirk, 2000) that differentiates between ‘metacognitive knowledge’ about one’s cognitive abilities and online monitoring of performance during laboratory tasks, which relates to ‘emergent awareness’ and ‘anticipatory awareness’. All patients exhibited poor insight for each awareness type relative to neurologically healthy controls; however, FTD patients were disproportionately more impaired than CBD and PSP patients on ‘emergent awareness’. Specifically, FTD patients were less able to monitor their errors on two separate tasks of executive function requiring sustained attention and response inhibition.

The relationship between the three putative awareness categories and neuropsychological and clinical rating variables across all patients was explored using linear regression. Metacognitive knowledge of awareness problems was predicted by SO ratings of behavioural and social impairments on the FrSBe, by the breakdown of goal-directed actions during the NAT and by reduced speed and flexibility of cognitive operations as assessed by verbal fluency (FAS test). Poor anticipatory awareness was also predicted by higher ratings of behavioural problems by caregivers on the FrSBe; but additionally, patients’ ability to accurately predict their performance was associated with impairments of mental flexibility, poor motor programming and increased sensitivity to interference and reduced environmental autonomy as measured by the FAB. Furthermore, a laboratory task of inhibitory dysfunction, the XY response inhibition task, demonstrated that increased impulsivity of responding was linked to poorer judgements of response accuracy in the future. Patients’ ability to detect errors as they occurred, described as emergent awareness, was predicted exclusively by sustained attention performance as measured by the SART.

A PCA of different items on the awareness interview demonstrated that discrete factor loadings emerged for different objects of insight: orientation; motor and perceptual awareness; thinking and language; and memory and attention. However, with regard to whether the three patient groups showed separable insight deficits across different domains of awareness, no such interaction emerged; patients showed a general impairment of awareness that was pervasive across all objects of insight.

Metacognitive awareness

Impaired appraisal of the cognitive deficits experienced by all patients is most likely related to prefrontal disruptions, common to all the three patient groups; therefore, the observed equivalent levels of impaired self-awareness are to be expected. Poor self-awareness across all patient groups was predicted by largely frontal executive measures which confirms the previously demonstrated linkage between this type of awareness deficit and frontal lobe disruption in both FTD patients (Souchay *et al.*, 2003) and Alzheimer’s patients (Starkstein *et al.*, 1992; Reed *et al.*, 1993). Recent evidence (Boxer *et al.*, 2006) also suggests that CBD patients show patterns of atrophy in both dorsolateral prefrontal cortices (DLPFC) and superior parietal areas suggesting that both maintaining a cognitive representation in working memory (associated with DLPFC activity) or accessing a mental content that reflects attributions of the self (associated with posterior parietal activation) (Vogele *et al.*, 2001) may underlie metacognitive deficits in CBD patients.

While movement disorder had been emphasized as a consistent feature across FTD, CBD and PSP, more recent evidence suggests that language symptoms are

considered common across the three patient groups as well (Kertesz and Munoz, 2004). With respect to language, another facet of metacognitive awareness that emerged, as part of the neuropsychological predictors of self-awareness in the current dataset, was verbal fluency. Poor fluency reflects an inability to maintain an effective retrieval strategy or to suppress interference from earlier memory associations; thus, potentially disrupting one’s ability to represent or access self-mental states. Aphasia often co-occurs as a secondary cognitive disturbance to the primary motor deficits in CBD, demonstrating that impaired cognitive flexibility in the language domain is related to the progression of the pathology. In PSP, patients have previously demonstrated poor initiation and search strategies on tasks of letter and category fluency and sentence completion (Esmonde *et al.*, 1996) and language deterioration is also present in FTD. The prevailing language problems in these patients and their observed verbal fluency deficit may also underpin patients’ reduced ability to formulate ideas about their cognitive limitations reflecting a lack of metacognitive insight.

The impaired metacognitive awareness also seen in PSP patients may initially seem at odds with the limited atrophy in the frontal areas of these patients; however, the midbrain, pons, thalamus and striatum all show extensive atrophy (Boxer *et al.*, 2006) and the likely consequence of this is frontal deafferentation that is secondary to interruption of frontostriatal feedback loops. In PSP patients, these disturbances to fronto-subcortical pathways most likely underlie their associated metacognitive insight problems.

Emergent awareness

Detecting errors as they emerged was the only type of awareness to differentially discriminate between clinical groups, with FTD patients disproportionately impaired. Emergent awareness has been linked to anterior cingulate cortex (ACC) and dorsolateral prefrontal (DLPFC) regions in an fMRI study of error processing (Hester *et al.*, 2005). Specifically, the ACC was active during detection of information about stimuli/responses but an important corollary to this activity was the subsequent initiation of the DLPFC for strategic implementation of post-error adjustments of behaviour. Volumetric MRI has recently identified ACC and DLPFC atrophy as well as orbitofrontal atrophy in FTD patients (Perry *et al.*, 2006). Consequently, the disproportionate deficit in emergent awareness in FTD patients in the current study is likely to be related to dysfunction in the very brain regions whose activations correlate with error processing.

Impaired emergent awareness has also been linked to sustained attention deficits in patients with frontal damage (McAvinue *et al.*, 2005). TBI patients with higher attentional lapses on the SART were less aware of committing an error. Consistent with this finding, in the

current study, impaired sustained attention was the only predictor of poor emergent awareness across all patients. It is noteworthy that a non-significant trend of increased lapses of attention was observed in the FTD group compared to the CBD and PSP (Table 1) which tentatively suggests that sustained attention problems may be a more prominent feature in FTD. Positron Emission Tomography (PET) studies (Sturm *et al.*, 1999, 2004) suggest that an extended right hemisphere network is involved in sustained attention including the right DLPFC and ACC and the right inferior parietal lobule with projections to the thalamus and noradrenergic brainstem targets. Damage to areas within this broader sustained attention network has been reported in FTD: these include the bilateral DLPFC damage reported by Perry *et al.* (2006) and, in another study, predominately right lateralized DLPFC atrophy in FTD patients (Rosen *et al.*, 2002). These findings support the conjecture that sustained attention is likely to be compromised in FTD patients and this may underlie the emergent awareness deficits observed in the current study. In contrast, although CBD patients are also afflicted by frontal pathology, Boxer *et al.*'s (2006) voxel-based morphometry approach identified greater frontal atrophy in the left hemisphere compared to the right suggesting that CBD patients' right hemisphere sustained attention networks are perhaps less disrupted than FTD patients. Similarly, PSP patients, with atrophy to midbrain structures and less extensive frontal atrophy, would be expected to show less problems of sustained attention with the caveat that even limited frontal atrophy or frontal disconnection syndrome is likely to give rise to some impairments relative to neurologically healthy controls, as we have observed. Overall, the more extensive disruption to the frontal cortices in the FTD patients is likely to contribute to deficits of sustained attention and emergent awareness more so than in CBD and PSP patients.

Anticipatory awareness

The composite scores from the prediction tasks (Online Anticipatory Awareness) indicated that each of the patient groups overestimated how they thought they could perform on cognitive tasks, compared to controls, who tended to underestimate compared to actual performance. This finding is consistent with that of Souchay and colleagues (Souchay *et al.*, 2003) who found that FTD patients significantly overestimated their predictions on a memory task. In contrast to online emergent awareness, anticipatory awareness has no specificity in terms of validation against neuroanatomical location. The ability to successfully anticipate performance accuracy involves a range of cognitive functions to which our regression analysis testifies. A particularly strong predictor of anticipatory awareness was performance on the FAB. Patients who were less able to switch flexibly between different subgoals, who exhibited impulsivity or poor inhibitory motor control, and suffered from increased sensitivity to interference were

the most inaccurate at predicting their cognitive performance. This diversity of cognitive impairments has been associated with equally diverse functional correlates, albeit largely involving frontal executive systems. For example, functional imaging studies have implicated frontopolar cortices as critical nodes in the circuit for maintaining and generating subgoals and for integrating subgoals with an ongoing primary task (e.g. Braver and Bongiolatti, 2002; Badre and Wagner, 2004); inhibitory motor control recruits distributed frontoparietal networks and subcortical areas including the basal ganglia during performance on the XY response inhibition task—a key predictor of anticipatory awareness in the current study (Kelly *et al.*, 2004), and impulsive behaviours and poor interference control is linked to the integrity and function of ventromedial and associated cortico–limbic pathways (e.g. Cato *et al.*, 2004). The fact that all three patient groups show deficits at this level of awareness suggests that distributed frontal disruption (through more extensive frontal atrophy in the case of FTD and CBD and through some frontal atrophy and/or frontal deafferentation in the case of PSP) may underlie the inaccuracies in anticipatory awareness seen in these patients.

Emotional dysfunction and awareness

Poor anticipatory awareness was associated with higher levels of depression on the HADS and poor metacognitive awareness was related to a lower empathic rating in all patients. Emotional disturbance and loss of insight has been investigated in the AD literature, though findings are inconclusive with some researchers reporting lower depression levels associated with less awareness (Starkstein *et al.*, 1992) and others failing to demonstrate a relationship (Vasterling *et al.*, 1995). The finding from the present study suggests that the relationship between emotional disturbances (such as depression and reduced empathic tendency) and loss of insight should be investigated further, as it suggests that preserved insight may be linked with lower emotional dysfunction. Additionally, in the present study both impaired metacognitive and anticipatory awareness was associated with poor recognition of emotional expression in faces. One important aspect of awareness is the personal relevance and emotional meaning evoked by one's mental contents, and it has been proposed that limbic–paralimbic pathways (Abu-Akel, 2003) are critical to evaluate the salience of emotional stimuli/responses that in turn, informs our decision making and social functioning via ventromedial–limbic interactions (Bechara *et al.*, 1994). It has been demonstrated that face-selective fusiform cortex may be enhanced by emotional processes mediated by the limbic system (Vuilleumier and Pourtois, 2006). We speculate that impaired connectivity between ventromedial, orbitofrontal areas and the limbic system, known to be implicated in facial emotional processes (Winston *et al.*, 2003), may give

rise to impaired emotional appraisal of faces by some of the patients in the current study. Poor evaluation of emotional expression in faces may weaken the emotional and social elements of their metacognitive knowledge and lessen their foresight and social judgement associated with anticipatory awareness.

Awareness in the control group

It is noteworthy that there are large discrepancies scores in the control group, particularly for the Frontal Systems Behavioural Scale, which is somewhat unusual as one would expect limited or no discrepancy between neurologically healthy controls and their significant others. We speculate that large discrepancies will arise between controls and significant others because (a) the significant other will assume ‘normality’ for a control participant and perhaps overestimate their capabilities, favouring a positive assessment for a neurologically healthy individual and (b) the self-ratings from the controls may be more realistic or perhaps, more self-critical, compared to SO ratings; together these perspectives may explain the large discrepancies. Nevertheless, it should be noted that the patients consistently over-estimated their performance/abilities irrespective of the control data.

Conclusions

Overall, the findings from the present study fit with theoretical and functional models of self-awareness that differentiate between Metacognitive Knowledge and Online Awareness (Emergent and Anticipatory) (Toglia and Kirk, 2000). Each patient group showed impairments across all the three types of awareness; although, FTD patients were disproportionately impaired on Online Emergent awareness compared to CBD and PSP patients. This finding is consistent with Rankin *et al.*’s (Rankin *et al.*, 2005) interpretation that FTD patients may have more severe damage to the prefrontal structures required for emergent awareness; recently imaging studies investigating online error processing suggest the DLPFC and the ACC are critical in this regard. The findings also relate to CAM, the neurocognitive model of Morris and Hannesdottir (Ryan *et al.*, 2006), with FTD patients exhibiting more severe ‘executive anosognosia’, as a consequence of more significant levels of frontal executive damage. All patient groups show deficits of metacognitive and anticipatory awareness relative to neurologically healthy controls. We propose that all patients have a deficit in maintaining a cognitive representation in working memory, driven by frontal executive processes or accessing a mental content that reflects attributions of the self-associated with more posterior parietal activation; this disruption to metacognitive awareness arises due to either direct frontal atrophy or through the breakdown of fronto-subcortical pathways. We speculate that more distributed executive and

frontal-subcortical disruption underlies anticipatory awareness; thus, any one deficit weakening cognitive flexibility, inhibitory motor control or interference control can reduce patients’ capabilities in terms of their foresight for cognitive and social judgements.

Clinical implications

The clinical and theoretical implications of this study are manifold. From a clinical perspective, this is the first study to our knowledge to systematically examine loss of insight in FTD patients in terms of Metacognitive Knowledge and Online Awareness. As a core criterion, this study takes the process of quantifying this symptom further. Furthermore, for CBD and PSP patients, it is clinically relevant for diagnosis, disease progression and effective assessment that both of these patient groups showed significant loss of insight, for both Metacognitive Knowledge and Online Awareness. Loss of insight can lead to a number of negative outcomes such as increased stress and caregiver burden (Seltzer *et al.*, 1997), poor patient–caregiver interaction (Hutchinson *et al.*, 1997) and poor medication compliance (McGlynn and Schacter, 1989). With regard to the assessment of loss of insight, it is clear from these findings that it must be investigated quantitatively using a multi-dimensional approach to elucidate the nature and correlates of this multifaceted phenomenon that is awareness. These findings also support theories that fractionate different elements of self-awareness functionally and neuroanatomically. It is vital that further research is conducted to further examine the neural, cognitive and emotional correlates of loss of insight in these patient groups, and the effect that unawareness has on caregivers.

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