Journal of Neurology (2023) 270:1880–1907
https://doi.org/10.1007/s00415-022-11518-9

REVIEW

Awareness impairment in Alzheimer's disease and frontotemporal dementia: a systematic MRI review

Michela Leocadi[1,5] · Elisa Canu[1] · Angela Paldino[1,5] · Federica Agosta[1,2,5] · Massimo Filippi[1,2,3,4,5]

Received: 31 August 2022 / Revised: 2 December 2022 / Accepted: 3 December 2022 / Published online: 13 December 2022

Abstract

This review aims to define awareness impairment and related disturbances in neurodegenerative diseases, including Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) spectrum of disorders. An update of the available scientific literature on the use of magnetic resonance imaging (MRI) in the study of awareness in these disorders is also offered. MRI plays an important role in the characterization of neurodegenerative signatures and can increase our knowledge on brain structural and functional correlates of awareness. In the reviewing process, we established a-priori criteria and we searched the scientific literature for relevant articles on this topic. In summary, we selected 36 articles out of 1340 publications retrieved from PubMed. Based on this selection, this review discusses the multiple terms used to define different or overlapping aspects of awareness impairment, and specifically summarizes recent application of MRI for investigating anosognosia, social cognition, including theory of mind and emotional processing, free will, and autonoetic awareness alterations in different neurodegenerative disorders, with most of these studies focused on AD and FTLD. This systematic review highlights the importance of awareness impairment and related domains in neurodegenerative disorders, especially in AD and FTLD, and it outlines MRI structural and functional correlates in these populations.

Keywords Neurodegenerative disorders · Alzheimer's disease · Frontotemporal dementia · Magnetic resonance imaging · Awareness · Systematic review

Introduction

Awareness can be defined as a mental state in which the perception of the external events is internalized [1]. It is not the simple acquisition of information about something, but reflects daily knowledge that allows an analysis of life situations (essential for human beings), starting from grounded connection to one's own mental states, beliefs, attitudes and lived experiences [2]. Awareness is essential to pursue everyday activities, it allows individuals to adjust their behavior according to the specific situation and to choose being engaged in tasks that suit their skills also considering their weaknesses. Impaired awareness has been extensively studied in several neurological and psychiatric disorders, and it has been observed to affect the well-functioning of distinct cognitive domains, such as memory and socio-emotional abilities [3]. In neurodegenerative disorders, impaired self-awareness is a common phenomenon, which can occur at different stages of the disease course, can vary consistently across disorders and can affect patients' and caregivers' life at different levels, such as in the activities of daily living, interpersonal relationships, emotional communication and processing [4]. From the clinical perspective, scarce awareness for one's own deficits can lead to poor adherence to pharmacological treatment, reduced financial management abilities, reduced driving safety and hazardous behaviors, with all these aspects leading also to legal consequences for both patients and caregivers [4]. For all these aspects,

✉ Massimo Filippi
filippi.massimo@hsr.it

1 Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Via Olgettina, 60, 20132 Milan, Italy

2 Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

3 Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy

4 Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

5 Vita-Salute San Raffaele University, Milan, Italy

the bulk of research on awareness impairment and related disturbances in the last years focused on neurodegenerative disorders, and specifically Alzheimer's disease (AD) and Frontotemporal Lobar Degeneration (FTLD), which are the most frequent disorders affecting adults also at a presenile age [5].

In the scientific literature, a variety of terms has been used to describe reduced awareness in neurodegenerative diseases, especially in patients with AD and FTLD. The most common examples are the following: 'lack of awareness or self-awareness', 'lack of consciousness', 'lack of insight', 'anosognosia', 'reduced autonoetic awareness', 'lack of free will'. These domains are deeply connected with the social aspects that modulate the relationships and the communication between patients and significant others, thus determining the link between awareness and other terms such as 'social cognition deficit', 'lack of empathy', 'theory of mind impairment', 'emotional processing deficits', 'inability to understand sarcasm', or 'impairment in moral reasoning'. However, a commonly accepted definition is not available yet, and several of these terms are used as synonyms of awareness, therefore generating ambiguity.

Nowadays, it is amply recognized that awareness does not reflect an unitary phenomenon and that its neuroanatomical correlates cannot be narrowed down to a single 'brain center' [6]. The most consistent neuroimaging literature with the use of magnetic resonance imaging (MRI) on the topic reports that 'self-awareness' is associated with the integrity of cortical midline structures, which represent a convergence zone for linking subcortical and lateral cortical regions and allowing bottom–up and top–down modulation between sensory, self-referential, and higher-order cognitive processing [7]. However, due to the ambiguity around the term "self-awareness", to date no previous studies elucidated the neural correlates of awareness alterations and its related constructs in detail.

Aim of this review is to provide an overview of research studies which adopted MRI to assess brain structural and functional correlates of awareness impairment in different neurodegenerative diseases, including AD and FTLD spectrum of disorders. Furthermore, an analysis of the importance of awareness, and its different constructs, was conducted in these disorders.

In the formal reviewing process, we established a-priori criteria to select dedicated articles that we summarized and discussed. Furthermore, this work offered the opportunity to overview the nomenclature used for defining and referring to awareness, in particular we criticized the extensive use of synonyms, which are erroneously used interchangeably. We finally commented on the consequences due to awareness loss or impairment in patients and on the resulting ethical implications in neurodegenerative disorders.

Materials and methods

Inclusion and exclusion criteria

Articles were selected according to predefined inclusion criteria: (a) studies focusing on awareness; (b) on neurodegenerative syndromes with awareness-related disturbances, such as AD, behavioral variant of frontotemporal dementia (bvFTD), Lewy body Dementia, primary progressive aphasia (PPA), amyotrophic lateral sclerosis (ALS), and progressive supranuclear palsy (PSP); (c) the use of structural and functional MRI; (d) on humans; (e) available in English and in full-text. We excluded: (a) articles that did not include the use of MRI as primary method of investigation; (b) articles not related to awareness; (c) studies on animals and other populations; (d) case reports, reviews, or meta-analyses.

Search strategy

A formal literature review was performed using PubMed database on relevant articles, published in peer-reviewed journals until December 2021 with the use of three macro areas: (1) awareness, (2) neurological disorder, (3) MRI. The final search line was the following: [(((((("self-consciousness") OR (consciousness)) OR (insight)) OR ("self-awareness")) OR (awareness)) AND ((((((((((bvFTD) OR ("behavioral variant of frontotemporal dementia")) OR (AD)) OR ("Alzheimer's disease")) OR (Alzheimer)) OR (PSP)) OR ("progressive supranuclear palsy")) OR (LBD)) OR ("Lewy body dementia")) OR (ALS)) OR ("amyotrophic lateral sclerosis"))) AND ((("magnetic resonance imaging") OR (MRI)) OR (MR))].

We explicitly filtered our research on PubMed by excluding reviews, animal studies, and articles not published in English language. We imported our research string in Rayyan Intelligent Systematic Review Tool (http://www.rayyan.qcri.org) [8] and, after duplicate removal, we obtained 1340 articles available for double-blinded title and abstract screening by two independent reviewers (M.L., A.P.). Once each reviewer reached a decision for all articles, they shared their decisions and discussed each case with conflict until consensus was reached, under the supervision of a third independent reviewer (E.C.). Finally, the reviewers reached a consensus for the eligibility of 43 articles for a subsequent unblind full-text screening. After full-text screening, only 36 articles were considered eligible for the aim of the study and were included in the present review (Fig. 1). In the Results section, we describe the findings from the 36 selected studies, which have been grouped and divided in macro-areas

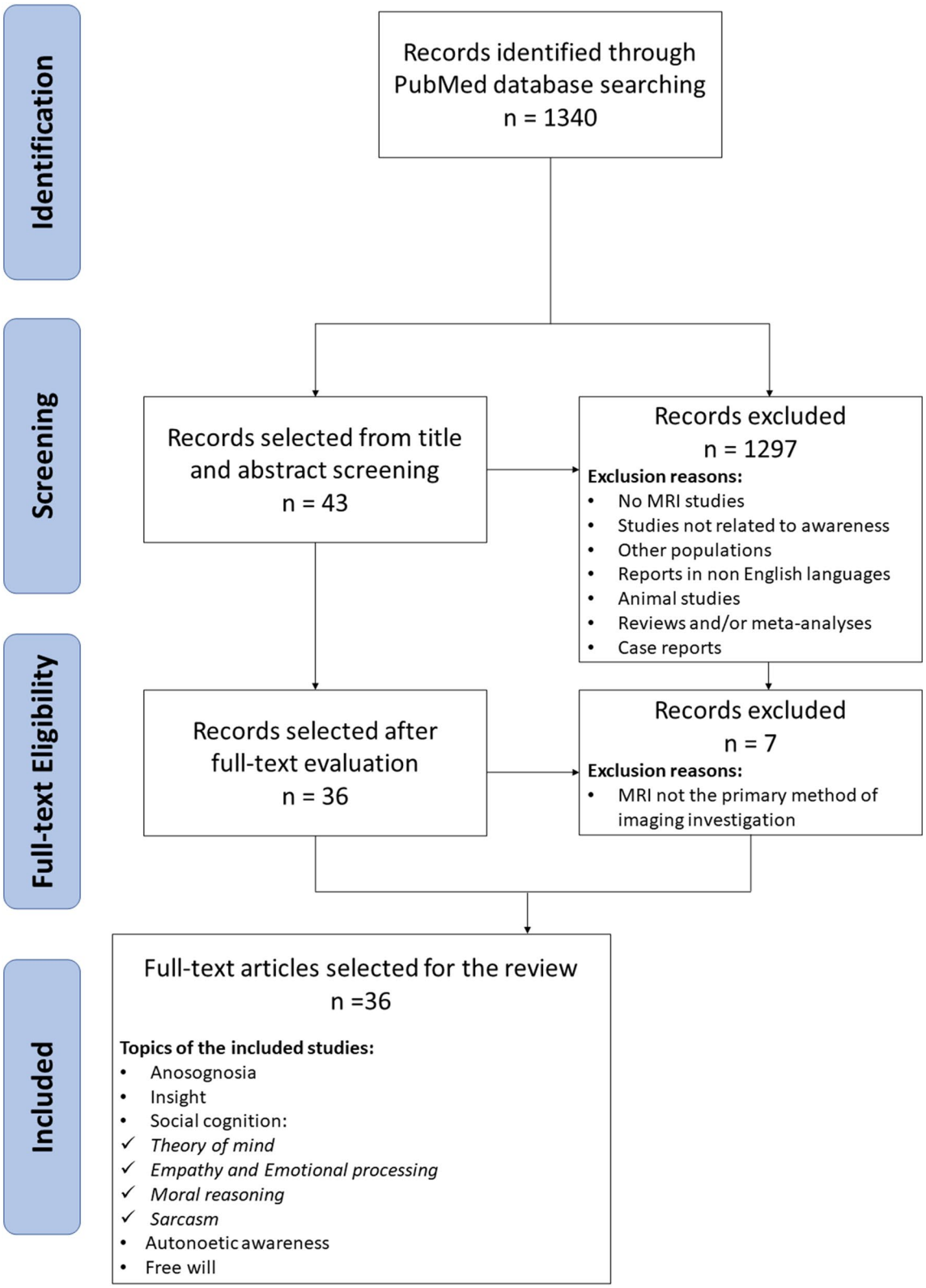

Fig. 1 Flow-chart of study selection. The diagram shows the detailed process of study selection according to PRISMA guidelines for systematic reviews and meta-analyses. *Abbreviations: MRI* magnetic resonance imaging

according to the different aspects of awareness. Specifically, we discussed our results by focusing on anosognosia, insight, social cognition, autonoetic awareness and free will (Fig. 2). All these studies and their main features have been also reported in Table 1.

Results

The following results are focused on several aspects of awareness impairment and related disturbances in distinct neurodegenerative diseases, investigated with the use of MRI. A glossary summarizing the main clinical features of each neurodegenerative disorders included

Fig. 2 Word cloud reflecting the extensive nomenclature used for defining and referring to awareness. This figure was created using WordClouds.com, which is a free online word-cloud generator

Table 1 Summary of the 36 studies selected for the reviewing process

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
Anosognosia					
1. Ries et al. [20]	-16 MCI -16 HC	***MRI:*** T1-weighted images, EPI T2*-weighted images, task-based fMRI (self-condition *vs* semantic condition) Techniques: whole-brain VBM and ROI-based fMRI analysis (ROIs: MPFC and PCC)	1. To investigate whether cortical midline structures are involved in self-referential processing 2. To demonstrate whether a self-appraisal fMRI task is sensitive to functional brain changes in association with impaired insight in MCI	- MCI showed attenuated cortical midline structures activity during self-appraisal condition; - Presence of a negative relationship between BOLD response during self-appraisal and self-awareness of memory deficits in MCI	Anosognosia for memory deficits (measured with IQCODE) IQCODE [84] is a 26-item questionnaire administered to informants of elderly patients and employed to assess cognitive decline. Scores range from 1 to 5
2. Amanzio et al. [23]	-29 AD (15 aware and 14 unaware of deficits)	***MRI:*** T1-weighted images, T2-weighted images, task-based fMRI (response inhibition task) Techniques: whole-brain fMRI analysis, and random effect ROI analysis (ROI: sub-region of the ACC)	To demonstrate that cingulate hypo-functionality predicts unawareness of deficits in AD patients	Compared to aware patients, unaware cases showed reduced task-sensitive activity in the right anterior cingulate area and in the rostral prefrontal cortex, reduced activity in the right post-central gyrus, in the associative cortical areas and in the cerebellum	Unawareness of deficits (AQ-D) AQ-D [85] scale is composed of 30 questions, divided into two sections (A and B), and it is used to discriminate aware and unaware patients. Final score is calculated by deducting the Form B scores from the Form A scores
3. Ries et al. [21]	-7 MCI -5 early AD -12 HC	***MRI:*** T1-weighted images, T2-weighted images, task-based fMRI (self-condition *vs* semantic condition) Techniques: whole-brain VBM and SBFC analysis (seed: MPFC)	1. To assess differences in memory self-appraisal in MCI and HC 2. To investigate changes in MPFC FC that correspond to impaired self-appraisal accuracy (specifically appraisal of current memory ability)	1. HC accurately assessed their own memory ability, but MCI and early AD showed variable accuracy in their memory self-appraisals 2. Altered MPFC FC explained variance in memory self-appraisal accuracy	Memory self-appraisal (MARS) MARS [86] assesses memory awareness in two domains: memory functioning and memory performance. Maximum possible score is 52 for both domains
4. Zamboni et al. [22]	-17 AD -17 MCI -17 HC	***MRI:*** T1- weighted images, EPI T2*-weighted images, task-based fMRI (Self condition/ Other condition) Technique: whole-brain fMRI analysis	To use task-related fMRI to directly explore the neural basis of self-awareness in MCI and AD patients in terms of differences in: 1. behavioral measures (discrepancy scores); 2. fMRI-related activation	1. AD had higher "Self-discrepancy scores" than HC and MCI 2. group-by-condition interaction: AD showed decreased activation of medial prefrontal and anterior temporal regions in the Self condition only	-Anosognosia (measured with AQ-D) -Self-awareness (questions regarding themselves or a study partner – Anderson Traits list), which comprises 555 personality-trait words [87]

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
5. Shany-Ur et al. [4]	-35 AD -21 bvFTD -7 rtFTD -8 svPPA -7 nfvPPA -46 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM	1. To characterize self-awareness for competency across multiple functional domains in patients with neurodegenerative diseases and HC; 2. To identify the structural neuroanatomical correlates of impaired self-awareness of functioning	1. bvFTD overestimated their competency for ADL, cognitive functioning, interpersonal functioning, and emotion regulation; rtFTD overestimated their interpersonal functioning; AD overestimated their cognitive functioning and emotion regulation; nfvPPA overestimated their emotion regulation and interpersonal functioning 2. The tendency to overestimate one's overall functioning corresponded with atrophy in bilateral, right greater than left, frontal and subcortical regions	Self-awareness (measured with PCRS) PCRS [88] consists of 30 items assessing functioning across four domains. Patients and informants are asked to rate each function on a scale of 1 to 5
6. Ford et al. [15]	-65 MCI -55 HC Longitudinal assessment: 18 months	***MRI:*** T1-weighted images Technique: whole-brain VBM	To determine whether awareness of cognitive deficits is associated with regional GM loss in MCI	In MCI, reduced awareness for cognitive deficits was associated with subtle GM loss of the medial frontal gyri	Awareness of cognitive deficits (AQ-D)
7. Spalletta et al. [16]	-36 aMCI (10 converters and 26 non-converters) Longitudinal assessment: 5 years	***MRI:*** T1-weighted images Technique: whole-brain VBM	To investigate the neuroanatomical correlates of awareness deficit in aMCI	At baseline, self-awareness of memory deficits was poorer in converters compared to non-converters and was correlated with reduced GM volume of the anterior cingulate, right pars triangularis of the inferior frontal cortex, and cerebellar vermis	Awareness of cognitive deficits (MIQ) MIQ [89] is a 33-item questionnaire designed to measure how much chronically ill patients give meaning to their illness. A 7-point scale is used to score every item
8. Perrotin et al. [29]	-23 AD -30 HC	***MRI:*** T1-weighted images, T2-weighted images, EPI T2*-weighted images, rs-fMRI Technique: SBFC (seeds: OFC, PCC) ***FDG-PET:*** [18F] FDG-PET images. Technique: whole-brain VBM	To understand the neural correlates of anosognosia for memory deficits in AD by combining regional brain metabolism and intrinsic FC	- AD patients underestimated their memory deficits; - Anosognosia in AD was related to hypometabolism in OFC and PCC cortices and reduced intrinsic connectivity between these regions and the medial temporal lobe	Anosognosia index (difference between subjective and objective memory scores)
9. Cosentino et al. [28]	-14 AD -20 HC	***MRI:*** T1-weighted images Technique: ROI-based volumetry analysis (ROIs: medial orbital, super frontal, and frontal pole; entorhinal, parahippocampal, and temporal pole; superior parietal and precuneus; caudal and rostral ACC, PCC; hippocampus, insula)	To investigate the correlates of metamemory in AD	Less accurate metamemory performance was associated selectively with reduced right insular volume in AD	Awareness of memory deficits (metamemory; FOK) FOK [90] is a metacognitive tool enabling people to estimate their future memory capacity

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
10. Amanzio et al. [24]	-15 probable bvFTD -8 possible bvFTD -30 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM ***PET:*** [18F] FDG-PET images	To explore the neural correlates of reduced awareness in IADL	A positive correlation between IADL and insular volume was found in bvFTD patients, indicating greater GM in more independent patients. There was a negative correlation between AQ-D score and cingulate volume in bvFTD, indicating atrophy in patients with less awareness	Awareness in IADL (AQ-D scale)
11. Vannini et al. [27]	-31 aMCI -251 HC	***MRI:*** T1-weighted images, rs-fMRI Technique: SBFC (seeds: PCC, OFC and IPL) **PET:** [18F] FDG-PET images	1. To investigate the neural correlates of anosognosia in aMCI in terms of (a) metabolic correlates and (b) intrinsic connectivity disruption between brain regions 2. To investigate group differences in terms of memory awareness	Greater anosognosia in aMCI was associated with: 1a. reduced glucose metabolism in PCC and hippocampus; 1b. attenuated FC between PCC, OFC and IPL; 2. aMCI patients had decreased memory awareness compared to HC	Anosognosia for memory deficits (calculated as the discrepancy scores between the objective and subjective measures of memory function)
12. Senturk et al. [17]	-21 early AD -26 aMCI	***MRI:*** Two consecutive T1-weighted images Technique: ROI-based Cortical thickness (FreeSurfer). ROIs: opercular, orbital, triangular parts of the inferior frontal gyrus, middle and superior frontal cortex, angular gyrus, supramarginal gyrus, parts of cingulate gyrus (ACC, anterior and posterior parts of middle cingulate cortex, and posterior and ventral parts of PCC), and superior parietal lobe in both hemispheres	To study the cognitive substrates of anosognosia in prodromal and early stages of AD 1. To investigate whether cognitive performances are lower in patients with anosognosia 2. To explore whether there is a relationship between the severity of anosognosia and cognitive functions in both patient groups and the total population 3. To assess correlations between cortical thickness in frontal–parietal–cingulate areas and anosognosia in these populations	1. In the overall patient population and considering only aMCI group, anosognosia patients scored worse in several cognitive tests than non-anosognosia patients; 2. AQ-D scores negatively correlated with cognitive performances in the total sample and in the aMCI group 3. No correlations between AD-Q scores and cortical thickness measures were found in all patients	-Anosognosia (AQ-D and CDR) -Insight (CIRS) CIRS [91] is a scale for the assessment of patient's awareness on the reason behind the medical examination, as well as the awareness of the presence of cognitive/functional deficits and disease progression. Total rating varies from 0 to 8

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
13. Sanchez-Benavides et al. [26]	-173 UD -568 SCD -1899 HC from the ALFA project	***MRI:*** T1-weighted images Technique: ROI-based and voxel-wise VBM (ROI: hippocampal cluster)	To analyze the clinical, cognitive and brain morphometric features of UD in comparison with SCD and HC	- No differences in anxiety and depression between HC and UD, while SCD were more depressed and showed more anxiety symptoms than HC - UD showed lower performance in the Memory Binding Test free recall than HC, but no differences compared to SCD; - UD showed increased GM volumes in right medial frontal and insular regions with respect to HC - Informant report of decline in UD and SCD was associated with lower left hippocampal GM volume; furthermore, it was also related to memory performance only in UD	-Self-awareness of cognitive decline
14. Guerrier et al. [18]	-30 probable early AD -35 HC	***MRI:*** T1-weighted images, EPI T2*-weighted images Technique: whole-brain VBM [18F] FDG-PET/CT images	To study the neural correlates of anosognosia by combining neuroimaging with neuropsychological evaluation	In patients: - GM atrophy and hypometabolism of the left dorsal ACC were correlated with the anosognosia deficits; - No relation was found between anosognosia and cognition	Anosognosia (CDS, French version) CDS [92] consists of 39 items rated on a 5-point Likert scale and permits respondents to rate how frequently they have experienced cognitive difficulties over the previous month
15. Antoine et al. [30]	*Study 1* -30 AD -19 HC *Study 2* -53 prodromal AD -15 HC	***MRI:*** T1-weighted images, EPI T2*-weighted images Technique: SBFC (seeds: bilateral posterior parahippocampus)	To assess the relationship between anosognosia for memory impairment and modifications of DMN sub-networks *Study 1* 1. Relationship between MARS score and connectivity with a parahippocampal seed *Study 2* 2. Relationship between a self-reported rating of memory performance and connectivity with hippocampal seed	Both studies: - Anosognosia was consistently related to disconnection within the medial temporal subsystem of the DMN in AD patients, subserving episodic memory processes; - Scores were also related to disconnection between the medial temporal and both the core subsystem (participating to self-reflection) and the dorsomedial subsystem of the DMN in AD patients	Study 1 -Memory Awareness (MARS) Study 2 -Self-reported rating of memory performance

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
16. Steward et al. [19]	-87 MCI	***MRI:*** T1- weighted images, T2 FLAIR images, T2-weighted fast spin echo Techniques: ROI-based VBM (ROIs: right and left mPFC, right and left inferior PFC, right insular cortex, ACC, MCC, PCC, left temporal cortex, right and left medial limbic cortex, left and right hippocampi, left lateral parietal cortex, left medial parietal cortex, the cerebellum) and supervised learning based multi-modal lesion segmentation technique	1. To study self-awareness in every day functioning in MCI 2. To examine the neuroanatomical correlates (in terms of GM volumetry and white matter lesion load) of unawareness for IADL deficits in MCI	1. 13–31% of MCI patients overestimated their current abilities; 2. Poor awareness was significantly related to reduce GM volume of the bilateral medial prefrontal cortex, middle and PCC, right insular cortex, and cerebellum	Self-awareness on 6 IADLs: Financial Management, Driving, Telephone Use, Grocery Shopping, Nutrition Evaluation, and Medication Management
17. Mendez et al. [32]	-30 AD -15 PCA	***MRI:*** T1-weighted images, T2-weighted images Technique: visual rating ***SPECT images***	To evaluate differences between PCA and AD in terms of: 1. Clinical features; 2. MRI findings	1. PCA had better verbal fluency, less memory difficulty, more depressive symptoms and greater insight of their illness than AD; 2. PCA patients showed occipito-parietal atrophy without detectable mesio-temporal atrophy	Awareness (as reported by the participants)
Insight					
18. Hornberger et al. [35]	-15 AD -24 bvFTD -18 svPPA -13 nfvPPA -11 lvPPA	***MRI:*** T1-weighted images Technique: whole-brain VBM	1. To compare insight across a large number of FTLD and AD patients 2. To explore GM correlates of the different insight domains in FTLD and AD	1. FTLD subtypes varied considerably for insight loss: bvFTD patients were the most affected, while the nfvPPA were the least affected; all other subgroups and AD showed milder but consistent insight loss; 2. Overall, insight loss correlated with ventromedial and frontopolar prefrontal atrophy; social interaction and emotion aspects of insight loss correlated with lateral temporal and amygdala atrophy, respectively	Insight (measured with the Insight questionnaire) The Insight questionnaire is composed of 28 items divided into five subscales assessing social interaction, emotion, diagnosis/treatment, language, and motivation/organization
Social cognition					

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
19. Synn et al. [39]	-18 AD -18 bvFTD -25 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM (FSL-VBM Toolbox)	1. To investigate the 'online' mental state attribution in bvFTD and AD cases using the Frith-Happé (ToM) animations 2. To delineate the neural substrates of ToM in the patient groups	1. bvFTD showed deficits in ToM classification compared to HC, while AD were impaired in the classification of Random and ToM trials Association between ToM deficits and carer ratings of affective empathy disruption in bvFTD, and with episodic memory dysfunction in AD 2. Overall ToM classification performance correlated with integrity of the right hippocampus and cerebellum in AD, and of the fronto-parietal, striatal regions and cerebellum in bvFTD	- Behavioral and socioemotional changes assessed with CBI and IRI CBI [93] is an 81-item informant-based survey designed to evaluate behavioral changes associated with neurodegenerative disorders. It assesses 13 functional/behavioral domains IRI [94] is a self-report questionnaire consisting of 28 items divided into four 7-item subscales, each assessing a different feature related to empathy - ToM (measured with Frith-Happé animations task) The Frith-Happé animations comprise three sets of geometric animations, each depicting a distinct form of motion: random, goal-directed, and ToM [95]. Participants undergo a dynamic evaluation of metallizing capacities
20. Giovagnoli et al. [38]	-14 bvFTD -14 HC	***MRI:*** T1-weighted images, FLAIR images Technique: visual rating	1. To study the qualitative features of ToM impairment in bvFTD 2. To explore the relationship between ToM impairment, disease progression, severity of dementia, and prefrontal cortex atrophy	1. bvFTD were impaired in faux-pas recognition, comprehension and awareness of factual details 2. Faux-pas comprehension failure was related to longer disease duration and prefrontal orbital atrophy	ToM (FPT) FPT [96] requires subjects to read a number of hypothetical dialogues and decide whether one of the characters made an impolite or rude remark
21. Kipps et al. [57]	-9 AD -26 bvFTD -16 HC Longitudinal assessment: a subgroup of patients and HC underwent MRI within 6 months	***MRI:*** T1-weighted images Techniques: whole brain VBM and ROI-based VBM analyses (ROIs: ACC, medial OFC, lateral OFC, amygdala, temporal pole, DLPFC)	1. To quantify the behavioral disturbances in bvFTD in social interaction 2. To link the above aspects to atrophy in socially relevant brain regions	1. Compared to the other groups, bvFTD were disproportionately worse at recognizing sarcastic comments rather than sincere comments. Their capacity to interpret negative emotions was impaired, and that had a major role in sarcasm recognition deficit 2. In bvFTD patients, sarcasm performance was linked to atrophy of the right lateral OFC, insula, amygdala and temporal regions	Social inference (using TASIT) TASIT [97] is a task that asks participants to assess the emotion and sincerity displayed by two protagonists in recorder vignettes. TASIT comprises three components: the emotion assessment test, the social-inference minimal test, and the social-inference-enriched test

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
22. Sturm et al. [52]	-27 bvFTD -33 HC	***MRI:*** T1-weighted images Technique: whole-brain cortical thickness and volumetry + physiological reactivity (polygraph)	1. To investigate the neural correlates of self-conscious emotional reactivity in bvFTD and HC 2. To examine whether neurodegeneration of pACC underlies diminished self-conscious emotion that was found in bvFTD and whether variability in pACC volume in HC is associated with individual differences in self-conscious emotion	1. Smaller right GM volume of pACC was a predictor of self-conscious emotion in both groups; 2. Smaller pACC volume was associated with attenuated physiological and behavioral self-conscious emotional reactivity (not specific to diagnosis)	Self-conscious emotional reactivity (embarrassing karaoke task *vs* sad film clip + physiological reactivity)
23. Chiong et al. [55]	-10 bvFTD -16 HC	***MRI:*** T1-weighted images, T2-weighted images, task-based fMRI (moral reasoning task: 7 dilemmas) Technique: whole-brain VBM and univariate task activation analysis	1. To demonstrate the presence of causal influence from the SN to the DMN in moral reasoning 2. To demonstrate activation of the DMN in personal moral reasoning 3. To find differences in DMN recruitment during deliberation about personal moral dilemmas between bvFTD and HC	1. FC from nodes of the SN to nodes of the DMN was observed during moral reasoning in HC; 2. The DMN is recruited when HC deliberate about personal moral dilemmas, but patients with bvFTD (with atrophy in the SN) give abnormally utilitarian responses to these dilemmas; 3. bvFTD have reduced recruitment of the DMN compared with HC when deliberating about dilemmas	Moral judgment (moral reasoning task) Participants were presented with vignettes describing a dilemma and then were asked to make judgments
24. Sollberger et al. [44]	-23 AD -28 bvFTD -16 svPPA -4 nfvPPA -12 CBS -19 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM	To investigate the correlation between overestimation or underestimation of one's capacity for empathic concern and specific patterns of focal brain damage	bvFTD and svPPA overestimated their level of empathic concern compared to HC. Overestimating one's empathic concern predicted the right anterior inferolateral temporal damage, whereas underestimating one's empathic concern showed no neuroanatomical basis in these patients	Self-awareness and empathy (IRI)

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
25. Downey et al. [62]	-29 bvFTD -15 svPPA -37 HC	***MRI:*** T1-weighted images, FLAIR images, and DTI images Technique: TBSS and VBM	To investigate the neuroanatomical basis of impaired social cognition in patients and the role of white matter correlates	bvFTD and svPPA patients showed comparably severe deficits for identification of canonical emotions and sarcasm, which correlated with white matter tract alterations affecting right frontotemporal connections The most robust DTI associations were: anterior thalamic radiation, fornix (emotion identification) and uncinate fasciculus (sarcasm identification). DTI associations were more consistent than corresponding GM associations	Social cognition (TASIT)
26. Shinagawa et al. [42]	-54 AD -31 bvFTD -13 svPPA -14 rtFTD -75 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM	1. To show changes in behavioral activation/inhibition in bvFTD, svPPA, rtFTD and AD 2. To assess the correlation between BIS/BAS score and regional atrophy pattern 3. To verify whether changes in BIS/BAS system correspond to neuropsychiatric symptoms	1. AD patients scored significantly higher in BIS score than bvFTD and HC groups; bvFTD patients scored significantly higher in BAS-D score than AD patients 2. BIS score correlated positively with right anterior cingulate, middle frontal gyrus volume, right precentral gyrus and left insula/operculum; 3. Higher self-reported depression would predict greater observer-reported behavioral inhibition and lower levels of behavioral activation	Behavioral activation/inhibition (BIS/BAS scale) The BIS/BAS [98] scale is a 24-item questionnaire that evaluates two motivational systems: the behavioral inhibition system (BIS) and the behavioral activation system (BAS). Each item is rated on a 4-point Likert scale
27. Hutchings et al. [47]	-10 AD -16 bvFTD -15 svPPA -17 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM	1. To determine how different dimensions of socio-emotional cognition are affected in bvFTD, svPPA and AD 2. To identify the neural correlates subserving the different dimensions of socio-emotional cognition	1. svPPA and bvFTD were rated lower on measures of empathy and emotion recognition compared to HC and AD. AD were rated similarly to HC in all dimensions. svPPA and bvFTD groups demonstrated reduced insight into socio-emotional dysfunction 2. GM intensity of the temporal regions correlated with empathy and emotion recognition. Social conformity was associated with the OFC and amygdala	Socio-emotional cognition evaluated by means of the SEQ (score was calculated by subtracting self-ratings from informant-ratings) SEQ [99] is a 30-item questionnaire designed to assess five dimensions of social functioning. Each item is rated from 1 (strongly disagree) to 5 (strongly agree)

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
28. Jastorff et al. [45]	*Study 1* -14 bvFTD -19 HC *Study 2* -16 young HC	***MRI:*** T1-weighted images, rs-fMRI (study 1) and task-based fMRI (emotion detection and categorization – Study 2) Techniques: whole-brain VBM, SBFC (seeds: ATL, IFG)	1. To investigate differences in emotion perception in bvFTD compared to HC 2. To investigate the anatomical correlation between emotion detection and emotion categorization impairment in bvFTD 3. To demonstrate whether ATL and IFG regions show differences in FC between patients and HC after correcting for whole-brain GM concentrations 4. To demonstrate whether ATL and IFG subtend information for emotion detection and categorization at the multi-voxel response pattern level in young HC	1. bvFTD patients were impaired in emotion detection and emotion categorization tasks; 2. The performance in the two tasks correlated with GM volume in two distinct brain regions: left ATL for emotion detection and left IFG for emotion categorization; 3. Left inferior frontal gyrus showed significantly reduced connectivity with the contralateral anterior insula, the contralateral amygdala and the contralateral ATL in bvFTD patients compared to HC; 4. Multivoxel pattern analysis in young HC demonstrated that both ROIs are involved in emotion detection, but only IFG was involved in emotion categorization	Emotion perception assessed through the presentation of emotional/neutral stimuli (participants had to judge whether the stimulus was emotional and, in that case, which emotion was displayed)
29. Wong et al. [56]	-14 AD -20 bvFTD -20 HC	***MRI:*** T1-weighted images Technique: whole-brain VBM	1. To investigate learning and memory of trust behavior in AD and bvFTD patients using a trust game paradigm 2. To examine the relationship between learning and memory for social trustworthy interactions and day-to-day financial vulnerability in AD and bvFTD patients and their neural correlates	1. Learning of trust/distrust and memory for social interactions was lower in patients compared to HC, but did not differ between patient groups. Both patient groups showed better memory for social than non-social interactions; 2. Better memory for social interactions was associated with lower financial vulnerability in AD, but not bvFTD. Learning and memory of social interactions was associated with medial temporal and temporoparietal atrophy in AD, while frontostriatal, insular, fusiform and medial temporal regions were implicated in bvFTD	Social cognition (trust game task)

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
30. Reus et al. [46]	-34 bvFTD -43 primary psychiatric disorders -28 neurodegenerative disorders (8 AD, 4 VD, 4 LBD, 5 PSP, 3 svPPA, 2 not specified, 1 HD, 1 CBS) Longitudinal assessment: 3 years	***MRI:*** T1-weighted images Techniques: whole-brain cortical thickness and subcortical volumes measurement (FreeSurfer)	To investigate whether the change in behavioral, cognitive and social cognitive symptoms over time differed between diagnostic groups (1), and which biomarkers (among CSF (2) and imaging biomarkers (3)) predicted rate of decline	1. Frontal behavioral symptoms worsened over time in bvFTD, they improved in psychiatric disorders and remained stable in other neurodegenerative disorders General and frontal cognitive decline was observed in bvFTD and other neurodegenerative disorders, but not in psychiatric disorders 2. Higher CSF NfL levels were associated with faster cognitive decline in all diagnostic groups 3. Smaller caudate volumes were associated with faster worsening of stereotyped behavior in all groups over time	Social cognitive symptoms
31. Toller et al. [41]	-29 AD -14 bvFTD -20 PSP -21 svPPA -19 nfvPPA -65 HC	***MRI:*** rs-fMRI Technique: ROI-based ICN analysis (seeds: right ventral anterior insula, PCC, right precentral gyrus)	1.To identify the relationship between SN connectivity and overt social behavior in HC and bvFTD; 2. To identify whether these relationships can be used to diagnose patients with early bvFTD	1. Higher FC in the SN, predominantly between the right anterior insula and both "hub" cortical and "interoceptive" subcortical nodes, predicted socioemotional sensitivity among HC, showing that socioemotional sensitivity is a behavioral marker of SN function 2. The continuity of this relationship in both HC and neurologically affected individuals highlights the role of socioemotional sensitivity as an early diagnostic marker of SN connectivity	Socioemotional sensitivity (RSMS) RSMS [100] comprises 13 items aimed at assessing sensitivity and responsiveness to subtly expressed emotions in face-to-face social interactions
Autonoetic awareness					
32. Thomann et al. [66]	-14 AD -15 MCI -24 HC	***MRI:*** T1-weighted images, T2-weighted images, Fast-Spin Echo images Technique: hippocampal volumetry (FSL-FIRST)	To investigate the potential association of hippocampal changes with deficits in semantic and episodic autobiographical memory in MCI and AD patients	In all patients, episodic but not semantic autobiographical memory loss was associated with morphological changes in the left hippocampus	Autonoetic awareness (measured with E-AGI) E-AGI is a semi-structured interview addressing both personal semantic data and autobiographical events from five different lifetime periods

Table 1 (continued)

Reference	Population (N)	Methods	Main outcome measures	Main findings	Main concepts
33. Buckley et al. [63]	***EAMI interview:*** -14 MCI -31 HC ***Aβ PET + MRI:*** -9 MCI -22 HC Longitudinal assessment: 3 years	***MRI:*** T1-weighted images Technique: whole-brain VBM ***PET:*** ^{11}C-PiB-PET imaging	1. To determine the extent to which neocortical Aβ, brain atrophy and APOE ε4 influence autobiographical memory, personal semantic memory, and autonoetic consciousness 2. To determine which memory variables (new learning, autobiographical memory and personal semantic memory) would explain variations in Aβ burden in MCI	- Autobiographical memory distinguished between MCI and HC, but did not relate to AD biomarkers; - Personal semantic memory was related to neocortical Aβ burden after adjusting for age and APOE ε4; - Autonoetic consciousness was not associated with AD biomarkers and was not impaired in MCI	Autobiographical memory, personal semantic memory, autonoetic consciousness
Free-will					
34. Lagarde et al. [71]	-18 bvFTD -21 PSP -18 HC	***MRI:*** T1-weighted images, T2-FLAIR images Technique: whole-brain VBM	1. To investigate the neural bases of grasping, imitation and utilization behaviors by correlating GM density to behavioral measures; 2. To verify whether these phenomena rely on a unique and homogeneous underlying mechanism or, on the contrary, on multiple, partially segregated components	1. Grasping and imitation are very frequent in both bvFTD and PSP patients, while utilization is rarer. In both patient groups, grasping correlated with GM density of the right superior frontal gyrus and inferior temporal gyri, while imitation correlated with changes of the right insula, left medial frontal gyrus and left precuneus. In both patient groups, environmental dependency was associated with the dysfunction of a frontoparietal network 2. Grasping and imitation behaviors could be dissociated from both neuropsychological and anatomical standpoints in both patients groups	Environmental dependency phenomena in relation to Free-will (as measured with Grasping, Imitation and Utilization behaviors)
35. Bertrand et al. [72]	-14 mild-to-moderate AD -20 HC	***MRI:*** T1-weighted images Technique: Regional cortical thickness (FreeSurfer)	To study the neural correlates of metamemory in mild-to-moderate AD in terms of regional cortical thickness	In AD and HC, less accurate metamemory was associated with reduced cortical thickness of the right PCC and right medial prefrontal cortex	Metacognition (FOK task)
36. Qian et al. [75]	-15 AD with delusions -15 AD without delusions	***MRI:*** T1-weighted images, EPI T2*-weighted images Technique: group-level PCA	To examine the relationship between delusions and FC of the resting brain	AD with delusions showed significantly reduced connectivity within the DMN and specifically of the left IPL	Delusions (NPI) NPI [101] is an informant-based survey evaluating the presence of neuropsychiatric symptoms over the previous month

in our search string, in results and in the discussion is reported in Table 2. Due to the research line findings and the final selected papers, results on awareness and corresponding MRI features are mainly related to AD and FTLD diseases.

Anosognosia

Anosognosia has been employed as a synonym of 'lack of awareness', and it can be defined as patient's unawareness of deficits resulting from brain disease or injury. Historically, it has been attributed to complete unawareness of hemiplegia in stroke patients, but later it expanded to include attenuated awareness of sensory, motor, and higher cognitive deficits [9].

In the last years, increasing attention has been paid to anosognosia in patients with mild cognitive impairment (MCI); this disorder is mainly characterized by a significant decline in memory and, often, in other aspects of cognition. Recent findings reported that these patients lack awareness of their functioning in everyday situations, especially in those activities which rely heavily on memory, and this aspect is related to greater conversion rates to overt AD [10]. However, in the last years increasing attention has been given also to anosognosia for non-amnestic complaints, such as word-finding and executive dysfunctions [11, 12]. Recent findings showed marked anosognosia in AD patients for their limitations regarding their general condition, and specifically for executive functions [12]; in this study, authors concluded that, when considering anosognosia for four domains of interest (namely memory, language, visuospatial and executive functions), anosognosia for executive functioning allowed a height discrimination between cases with and without dementia. Furthermore, recent studies focused on the fact that, in preclinical AD and very early in the disease process, patients might paradoxically experience heightened awareness for cognitive deficits even without objective measure at neuropsychological testing, and this phenomenon is called 'hypernosognosia' [13, 14]. Specifically, studies on preclinical AD cohorts comparing reports on cognitive complaints of normal individuals with amyloid pathology highlighted that amyloid positive subjects exhibited marked and higher memory and linguistic complaints than what was reported by their caregivers [13]. A recent study [14] showed that asymptomatic individuals harboring amyloid pathology had heightened self-awareness for their memory problems, while MCI patients with amyloid pathology demonstrated anosognosia for memory impairment in turn. These findings suggest a possible role of amyloid pathology in modulating self-awareness changes over the disease progression. However, hypernosognosia is still an emerging concept in research, and neuroanatomical studies assessing its brain correlates are still lacking.

Table 1 (continued)
Abbreviations: Aβ Beta-amyloid, *ACC* anterior cingulate cortex, *AD* Alzheimer's disease, *ADL* zctivities of daily living, *aMCI* amnestic subtype of Mild Cognitive Impairment, *APOE* Apolipoprotein E, *AQ-D* Awareness of Deficit Questionnaire-Dementia scale, *ATL* anterior temporal lobe, *BAS* Behavioral Activation System, *BIS* Behavioral Inhibition System, *BOLD* blood-oxygen-level-dependent imaging, *bvFTD* behavioral variant of frontotemporal dementia, *CBI* Cambridge Behavioral Inventory-Revised, *CBS* corticobasal syndrome, *CDR* Clinical Dementia Rating Scale, *CDS* Cognitive Difficulties Scale, *CIRS* Clinical Insight Rating Scale, *CSF* cerebrospinal fluid, *CT* computed tomography, *DMN* default mode network, *DLPFC* dorsolateral prefrontal cortex, *DTI* diffusion tensor imaging, *E-AGI* Erweitertes Autobiographisches Gedachtnis Inventar, *EAMI* Episodic Autobiographical Memory Interview, *EPI* echo-planar imaging, *FC* functional connectivity, *FDG* Fluorodeoxyglucose, *FIRST* FMRIB's Integrated Registration and Segmentation Tool, *FLAIR* Fluid-attenuated inversion recovery, *FOK* Feeling of Knowing, *FPT* Faux pas task, *FSL* FMRIB Software Library, *FTD* Frontotemporal dementia, *FTLD* Frontotemporal lobar degeneration, *GM* grey matter, *HC* healthy controls, *HD* Huntington's disease, *IADL* Instrumental Activities of Daily Living, *ICN* intrinsically connected network, *IFG* inferior frontal gyrus, *IPL* inferior parietal lobule, *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly, *IRI* Interpersonal Reactivity Index, *LBD* Lewy Body dementia, *lvPPA* logopenic variant of primary progressive aphasia, *MARS* Memory Awareness Rating Scale, *MCI* Mild cognitive impairment, *MIQ* Memory Insight Questionnaire, *MPFC* medial prefrontal cortex, *MRI* magnetic resonance imaging, *NfL* neurofilaments, *nfvPPA* non-fluent variant of primary progressive aphasia, *NPI* Neuropsychiatric Inventory, *OFC* orbitofrontal cortex, *pACC* pregenual anterior cingulate cortex, *PCA* posterior cortical atrophy or Principal Component Analysis, *PCC* posterior cingulate cortex, *PCRS* Patient Competency Rating Scale, *PET* Positron Emission Tomography, *PFC* prefrontal cortex, *PiB* Pittsburg compound-B, *PSP* progressive supranuclear palsy, *ROI* region of interest, *rs-fMRI* resting-state functional magnetic resonance imaging, *RSMS* Revised-Self-Monitoring-Scale, *rtFTD* right temporal variant of FTD, *SBFC* seed-based functional connectivity, *SCD* subjective cognitive decline, *SEQ* Socio-Emotional Questionnaire, *SN* salience network, *SPECT* single-photon emission computed tomography, *svPPA* semantic variant of primary progressive aphasia, *TASIT* Awareness of Social Inference Test, *TBSS* Tract-Based Spatial Statistics, *ToM* Theory of Mind, *UD* unaware decliners, *VBM* voxel-based morphometry, *VD* vascular dementia

A few neuroimaging studies unraveled the structural brain correlates of anosognosia in the different phases of AD [4, 15–19]. Compared to healthy individuals, patients with MCI showed atrophy in temporal and anterior portions of the brain, and more reduced awareness of cognitive deficits was associated with lower volume in the medial frontal gyri [15]. MCI and AD patients showed attenuated cortical midline structures activity during self-appraisal tasks (e.g., participants were required to make decisions about whether the presented trait adjectives described them or not) [20–22], which was associated with the reduced anosognosia for their cognitive deficits [20, 21]. Another study, which included amnestic MCI (aMCI) and early-stage AD patients, showed that, when considering the whole sample, patients with anosognosia had a relatively worse cognitive performance (in terms of episodic and working memory,

Table 2 Clinical features of neurodegenerative disorders included in the present review

Neurodegenerative disease	Clinical profile
AD	AD is the most common neurodegenerative disorder, with a progressive, irreversible, and incurable disease course. In its classical presentation, AD is characterized by episodic memory deficits, temporal and/or spatial disorientation, and visuospatial deficits. The loss of independence in daily life activities determines the presence of dementia. Behavioral disturbances can occur in the later stages ***Atypical presentations:*** All these patients have usually a younger disease onset compared to classical AD cases 1. PCA: it is the visual variant of AD. These patients show progressive visuo-spatial disturbances, mainly characterized by visual agnosia and difficulties in analyzing complex visual information 2. Frontal variant: it is characterized by behavioral disturbances, and by attentive and executive dysfunctions 3. For the linguistic variant of AD, see PPA
MCI	MCI is a clinical and heterogeneous condition considered the prodromal phase of various disorders (such as AD, LBD, FTD, Parkinson's disease, vascular dementia, and depression). MCI patients with an amnestic presentation (isolated or associated with any other cognitive dysfunctions) are more likely to develop AD. Compared to AD cases, these patients are independent in their daily life activities
bvFTD	bvFTD is the second most common neurodegenerative disorder after AD. It presents with a constellation of behavioral and cognitive symptoms: progressive changes in social conduct, lack of insight and empathy, apathy, disinhibition, impairment in emotional processing, prevalent attentive and executive dysfunctions with spared memory and visuospatial abilities The diagnosis is supported by neuroimaging evidence of alterations at the frontal and/or temporal lobes
LBD	LBD is characterized by progressive cognitive decline of attention, executive and visuo-spatial skills, which interferes with social and occupational activities. Furthermore, patients present with fluctuating cognition (variation in attention and alertness), recurrent visual hallucinations, and motor manifestations of atypical parkinsonism. Finally, they might show rapid eye movement sleep behavior disorder and severe neuroleptic sensitivity
PPA	PPA is a disorder which at onset is prevalently characterized by difficulties in the language domain 1. nfvPPA: patients show agrammatism in language production, effortful, halting speech with inconsistent speech sound errors and distortions. The diagnosis is supported by neuroimaging evidence of alterations at the left posterior fronto-insular gyrus. The underlined pathology of this variant is usually FTLD 2. svPPA: patients show impaired naming, single-word comprehension, and object knowledge. The diagnosis is supported by neuroimaging evidence of alterations at the left anterior temporal lobe. The underlined pathology of this variant is usually FTLD 3. lvPPA: patients show primary deficits of word retrieval and oral repetition of sentences or phrases. The diagnosis is supported by neuroimaging evidence of alterations at the left posterior perisylvian or parietal gyri. The underlined pathology of this variant is usually AD
ALS	The diagnosis of ALS requires the presence of progressive lower and upper motor neuron deficits in at least one limb or region of the body, and lower motor neuron deficits as defined by clinical examination and/or by electromyography in two body regions (bulbar, cervical, thoracic, lumbosacral) Subtle cognitive and behavioral disturbances occur in almost 50% of ALS cases during the disease course. These deficits, such as attentive-executive dysfunctions, fluency impairment and apathy, overlap with those presented by most of the FTLD disorders
PSP	PSP patients present four core symptoms: ocular motor dysfunction, postural instability, akinesia, and cognitive impairment. This latter is characterized by language and executive dysfunctions that could be associated with behavioral disturbances
CBS	CBS is a clinical disease characterized by asymmetrical cortical signs (limb apraxia and cortical sensory deficits), myoclonus and basal ganglionic signs (asymmetric limb rigidity, parkinsonism, and dystonia), and by resistance to levodopa. The neuropsychological profile is characterized by apraxia, visuospatial disturbances, executive dysfunctions, and behavioral alterations

Abbreviations: AD Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *bvFTD* behavioral variant of frontotemporal dementia, *CBS* corticobasal syndrome, *FTLD* frontotemporal lobar degeneration, *LBD* Lewy Body dementia, *lvPPA* logopenic variant of PPA, *MCI* mild cognitive impairment, *nfvPPA* nonfluent variant of PPA, *PCA* posterior cortical atrophy, *PPA* primary progressive aphasia, *PSP* progressive supranuclear palsy

and executive functions) than patients without anosognosia, and that this worse performance was also observed in the aMCI sub-group when considered alone [17]. Interestingly, levels of anosognosia in both patient groups were not associated with their structural brain changes as investigated with cortical thickness measurement, and authors inferred that they might instead be related to brain functional alterations. Conversely, in an early AD cohort, other studies showed that, regardless the presence of other cognitive disturbances, lower scores in tests measuring anosognosia were associated with atrophy, decreased brain functional connectivity and/or hypometabolism of the dorsal anterior cingulate cortex (ACC) [18, 23] and parieto-temporal regions [23], and to atrophy of the cerebellar vermis, left postcentral gyrus, and right fusiform gyrus [18]. A 5-years longitudinal study comparing MCI converters and non-converters to AD showed that, greater anosognosia accumulated in converters. Specifically, a total index of illness awareness deficit in converters was correlated with reduced grey matter (GM) volume of the cerebellar vermis, a region known to be functionally linked to frontal regions, including midline structures [16].

Poor awareness in activities of daily living

A recent study observed that 13–31% of MCI patients overestimated their abilities on instrumental activities of daily living (IADL) and poor awareness on these activities was related to reduced volume of bilateral medial prefrontal cortex, middle and posterior cingulate cortices (PCC), right insula and cerebellum [19]. On the other hand, lower IADL scores in bvFTD cases was observed to be associated with reduced insular volume, with the presence of further atrophy of medial prefrontal, mid-cingulate, cerebellum and cuneus, in less aware patients [24]. Another study which targeted patients belonging to the AD and FTLD *spectra* in comparison with healthy subjects highlighted that all these patients showed the tendency to overestimate their overall functioning, and this overestimation (obtained as a discrepancy between caregivers' and subjective evaluations) was associated with atrophy of frontal and subcortical regions (with right greater than left involvement). When comparing self-awareness in all patient subgroups (AD, bvFTD, right-temporal variant of FTLD [rtFTD], semantic variant of PPA [svPPA] and non-fluent variant of PPA [nfvPPA]) specific findings emerged. BvFTD patients overestimated their overall functional competency, and their competency in each functional domain (such as capacity in IADL, cognitive functioning, emotional regulation and interpersonal functioning), AD patients their cognitive functioning and emotion regulation abilities, rtFTD patients their interpersonal functioning, and PPA patients their emotion regulation and interpersonal functioning [4].

Poor awareness of memory deficits

Anosognosia for memory deficits is common in patients with AD and may be present in early predementia stages [25]. This problem has been retrieved also in psychometrically normal individuals without self-awareness of cognitive decline (unaware decliners, [UD]). A recent study [26], which focused on clinical, cognitive and brain morphometric differences between UD and patients with subjective cognitive decline (SCD), found no differences in terms of neuropsychiatric symptoms (anxiety and depression) in the two groups. UD and SCD had similar memory performances, which were poorer than those of controls, and right medial frontal and insular atrophy was observed in UD compared to controls. Informant report of decline in both UD and SCD was associated with lower left hippocampal GM volume, but it was related to memory performance only in UD.

Hypometabolism in the PCC and in the hippocampus has been associated with reduced awareness of memory deficits in aMCI, and to decreased functional connectivity between PCC, orbitofrontal and inferior parietal cortices [27]. These findings are in line with a 5-years longitudinal study, which observed that self-awareness of memory deficits was poorer in aMCI converters than in non-converters, and was correlated to reduced GM volume of the right ACC and right inferior frontal gyrus [16]. Similar findings were retrieved in a population of AD patients: as expected, they underestimated their memory deficits, and anosognosia was related to reduced right insular volume [28], orbitofrontal and PCC hypometabolism [29], and reduced functional connectivity between these regions, mainly those belonging to the default mode network (DMN) [29, 30].

Another study investigated anosognosia differences between posterior cortical atrophy (PCA) and typical AD cases. PCA is an insidiously progressive, complex visual syndrome associated with atrophy and/or hypometabolism of the parietal and occipital cortex [31], which is considered the visual variant of AD. The study showed that, compared to AD, PCA patients had preserved awareness of their deficits [32], likely due to their relative sparing of mesial temporal regions.

Summary

- Anosognosia is a synonym of lack of awareness, and it can be defined as a patient's unawareness of deficits resulting from brain disease or injury.
- In MCI and AD patients, anosognosia usually regards memory complaints; recent findings highlighted the importance of anosognosia for non-amnestic deficits, with anosognosia for executive problems being a good candidate to detect dementia cases.

- In preclinical AD, patients can experience hypernosognosia for cognitive deficits early in the disease course; however, neuroanatomical studies are lacking.
- Both AD and FTLD patients tend to overestimate their overall functioning; overestimation is associated with atrophy of frontal and subcortical regions (right greater than left involvement).
- Unawareness of memory deficits is related to atrophy in right medial frontal and insular cortices in UD, GM loss and/or hypometabolism of hippocampus and mesial temporal regions in aMCI, and reduced functional connectivity between mesial temporal and other DMN regions in AD patients.
- In PCA, which is a rare presenile variant of AD, awareness is preserved likely due to a sparing of mesial temporal cortex.

Insight

In psychology, the definition of insight comprehends the recognition of the consequences of one's behavioral actions resulting from a pathological state. Even though they are often used interchangeably, aspects of 'awareness' are narrowed down to an 'object' (e.g., cognitive deficits), while aspects of 'insight' are instead directed at the wider 'phenomenon' (e.g., clinical condition and its consequences) [33]. Altered insight may affect cognitive and behavioral domains differentially, and several findings reported that, among neurodegenerative diseases, it is more characteristic of FTLD rather than AD patients [34]. Specifically, FTLD patients demonstrate the most consistent loss of self-awareness and insight, as measured with comprehensive behavioral rating scales, which are administered to both patients and their caregivers. On the other hand, AD patients show less discrepancies between their own judgement and those of their caregivers.

Due to the greater prevalence of insight loss in the FTLD spectrum, increasing attention has been paid to these populations in the last years, even though only a few studies explored its neural correlates. A quite recent neuroimaging study, which focused on both AD and FLTD, employed a novel questionnaire to investigate insight differences in these populations [35]. FTLD subtypes (bvFTD, svPPA, nfvPPA) varied considerably in terms of insight loss: bvFTD patients were the most affected, followed by svPPA and AD patients, while the nfvPPA cohort was relatively spared. In general, insight loss was associated with ventromedial and frontopolar prefrontal atrophy, while other regions appeared to be specific for certain insight deficits: social interaction (social appropriateness and inhibitory functioning) and emotion insight loss (which relates to sympathizing with other people or understanding other people's emotions), for instance, correlated with lateral temporal and amygdala atrophy, respectively.

Summary

- Loss of insight is the inability to identify presence and severity of disease symptoms and to understand the consequences of one's behavior.
- It is a phenomenon severely affected in bvFTD, and mildly in AD.
- Among the FTLD spectrum, bvFTD are the most affected in terms of insight loss, followed by svPPA. Insight in nfvPPA cases is instead relatively spared.
- The neural correlates of insight loss are not yet well known, but a few studies identified them in the alterations of ventromedial and frontopolar prefrontal cortices.
- Certain insight deficits, such as social interaction and emotion insight loss, are associated with lateral temporal and amygdala atrophy, respectively.

Social cognition

Social cognition refers to a variety of processes which enable human beings to interact with their equals and be aware of their intentions and thoughts [36]. Social cognition encompasses implicit and explicit cognitive processes which enable individuals to interact and understand the social world. Social interaction is therefore linked to the processing and recognition of social and emotional signals (emotional processing), social knowledge awareness (e.g., social norms, and therefore moral reasoning), and social information processing (theory of mind [ToM]). The recognition of one's own emotions is an important signal of the internal state, and it is pivotal for guiding social behavior: here lies the link between self-awareness and social cognition [37]. Social cognition can be divided in different domains, and hereafter we report several findings from different studies targeting its distinct aspects: ToM, empathy and emotional processing, moral reasoning, and sarcasm.

Theory of mind

ToM can be described as the capacity to recognize and understand one's own or others' mental states [38]. People who lack ToM skills have difficulties in understanding social situations, and in being aware of all the subtle aspects of human interactions (e.g., persuasion, metaphors, or lies) [38].

A few neuroimaging studies attempted to describe ToM neural correlates in both bvFTD and AD patients [38, 39]. A first study, which employed a Faux-pas Task to assess features of ToM in bvFTD patients only, highlighted that in these patients ToM is mainly characterized

by a misinterpretation of other's mental states and concrete thinking, and is related to disease progression and atrophy of orbital and dorsolateral prefrontal areas [38]. Another study, which compared bvFTD to AD patients, showed that bvFTD had a specific deficit in ToM processing, which was associated with structural abnormalities of a distributed network, including medial prefrontal, frontoinsular, striatal, lateral temporal and parietal regions; while AD cases showed low accuracy in both random and ToM trials, which was rather due to episodic memory dysfunction and hippocampal involvement [39].

These studies suggest that ToM impairment in bvFTD patients is explained by the vulnerability in brain networks implicated in social cognitive functioning while, on the other hand, AD patients have ToM impairment of the same magnitude as in the former group, but their deficits seem to be secondary to memory dysfunctions.

Empathy and emotional processing

In the last years, increasing attention has been paid to empathy and emotional processing alterations among neurodegenerative disorders, especially in bvFTD and AD patients, with the salience network (SN) being a specific target of investigation for socioemotional functioning [40–42]. Early functional changes in the SN are associated with impairment in socioemotional sensitivity in patients with bvFTD, and to a lesser extent in AD, svPPA and PSP. Specifically, PSP patients, which manifest bvFTD-like behavioral symptoms, have subcortical alterations linked to changes in SN functional connectivity [41].

The link between awareness, empathy and emotional processing relies on the human ability to analyze internal emotional states; when this capacity is compromised, it is also likely that the person misinterprets other people' feelings and behavior, therefore acting inappropriately. Specifically, empathy is a complex social behavior, which involves the subjective emotional contamination induced by others' emotions, and the ability to differentiate between the proper feelings and the feelings expressed by others. This ability underpins accurate socioemotional self-awareness [43].

A quite recent study showed that patients with bvFTD and svPPA overestimated their level of empathic concern compared to controls; this altered feature predicted, at the cortical level, right anterior infero-lateral temporal damage [44]. On the other hand, emotion detection and categorization performances, which are lower in bvFTD compared to controls, were associated with GM volume loss of the left anterior temporal and left inferior frontal gyri, respectively [45, 46]. Unfortunately, due to small sample sizes, comparisons with other neurodegenerative disorders included in the study, such as vascular dementia, LBD, PSP and corticobasal syndrome (CBS), were not performed. All these patients were considered for the analyses as a whole group and not separately.

One study focused on socio-emotional dimensions (e.g., empathy, emotion recognition, and social conformity) and how these are differentially impacted in AD, bvFTD and svPPA patients [47]. Empathy, socio-emotional functioning and emotion recognition were found to be compromised in bvFTD and svPPA patients compared to controls and patients with AD [47]; in fact, AD patients were rated similarly to controls in all dimensions. Moreover, in bvFTD and svPPA, emotion recognition and empathy impairment were associated with atrophy of the left temporal pole, while impaired social conformity was associated with volume loss of orbitofrontal cortex and amygdala.

An interesting aspect of bvFTD cases is their difficulty in recognizing situations that would typically elicit self-conscious emotions, such as embarrassment, guilt, or pity [48, 49]; when put in laboratory settings, these patients have diminished physiological and behavioral self-conscious emotional reactivity [50, 51]. In one study, authors observed that attenuated physiological and behavioral self-conscious emotional reactivity during an 'embarrassing karaoke task' was associated with smaller right posterior ACC volume in bvFTD [52].

Moral reasoning

Moral reasoning is a mental process that individuals carry out to make a judgment about what action is morally right [53]. It is a complex higher-order social cognitive process that shares mechanisms with ToM and empathy, and it depends in part on accessing social rules [54].

A study [55] focused on functional brain activity during moral reasoning showed that, during deliberation about moral dilemmas, the SN has a modulatory role on DMN activation; however, this directed functional connectivity is diminished in bvFTD compared to controls, which might explain in turn why these patients provide abnormal utilitarian responses to proposed dilemmas.

During a functional MRI (fMRI) "Trust Game" paradigm, participants with AD and bvFTD were asked to invest virtual money with counterparts who acted either in a trustworthy or untrustworthy way over repeated interactions [56]. Learning of trust/distrust and memory for social interactions were impaired in patients compared to healthy controls, but did not differ between patient groups. Better memory for social interactions was associated with lower financial vulnerability in AD and linked to the integrity of medial temporal and temporoparietal cortices; on the other hand, while deciding for money investments, for bvFTD cases, memories of untrustworthy behavior were

considered equal to those of trustworthy actions and were linked to fronto-striatal and insular damage.

Sarcasm

The term sarcasm can be considered as a form of bitter irony specifically used to belittle and debase the interlocutor. However, irony is easier to understand, it makes a total distortion of the literal meaning of words, while sarcasm is a voluntarily derision of what is reported. The understanding of sarcasm is a complex process requiring appreciation of both the facts of a situation and the intention of the speaker, and it is communicated using facial affect and altered prosody [57, 58]. In fact, sarcastic intent is straightforward to manipulate, and its detection can be reliably assessed [59]. Brain injured patients, with ventromedial or orbitofrontal lesions [60], particularly in the right hemisphere, perform poorly on tests of sarcasm detection which correlates with both empathic ability and the capacity for affective processing [61].

The relationship between sarcasm and awareness lies on the assumption that sarcasm interpretation requires the integration of statement content with discordant paralinguistic cues, such as face expression or vocal prosody to accurately determine the speaker's true intent. Not being aware of what the speaker is saying could lead to a lack of understanding of the actual communication, and not interpreting correctly may result in an incorrect behavioral response of the patient.

Patients with bvFTD are disproportionately worse at recognizing sarcastic rather than sincere comments compared to healthy controls and patients with AD [57]. A study on bvFTD and svPPA highlighted that sarcasm performance (i.e., the right interpretation of sincere intent) was linked to regional GM volume of right anterior temporal and orbitofrontal cortices in all patients. Additionally, bvFTD and svPPA patients showed comparable severe deficits of emotions identification and sarcasm, and these deficits were correlated with white matter tract alterations affecting right frontotemporal connections [62].

Summary

- Social cognition enables individuals to interact and understand the social world, and to understand their own intentions.
- In bvFTD patients, ToM impairment is mainly characterized by a misinterpretation of other's mental states and concrete thinking, and is related to atrophy in orbital and dorsolateral prefrontal areas.
- ToM impairment in bvFTD can be explained by affective interpretation disruption, while it is explained by episodic memory dysfunction in AD patients.
- The SN is a key network supporting socioemotional functioning and its functioning is a prognostic marker to detect patients at the early stage of bvFTD.
- BvFTD and svPPA patients overestimate their level of empathic concern, and this predicts right anterior inferolateral temporal damage. BvFTD and svPPA patients show impairment in emotion recognition and empathy, which is associated to atrophy of the left temporal pole. Social conformity is associated to orbitofrontal and amygdala structures integrity.
- During a moral reasoning task, nodes of the SN influence nodes of the DMN, but this functional connectivity is reduced in bvFTD, who tend to give utilitarian responses.
- Since bvFTD patients are impaired in their capacity to interpret negative emotions, they are worse at recognizing sarcastic rather than sincere comments compared to AD and controls, and this is associated with atrophy of right lateral orbitofrontal, insula, amygdala and temporal regions.

Autonoetic awareness

Autonoetic awareness can be defined as a branch of awareness accompanying subjective re-experience of an event, and the mental capacity to travel forwards and backwards in time [63, 64]. It refers to memory of past and recent events, therefore to episodic memory. Autonoetic awareness is one fundamental property of this type of memory, together with the subjective sense of time and the connection with the self [65].

Autobiographical memory, which involves subjective time and autonoetic awareness [66], is commonly impaired in patients with MCI and AD, and a few recent neuroimaging studies have focused on its neural correlates. A study [66] observed that episodic, but not semantic, autobiographical memory impairment was associated with morphological changes in the hippocampus, primarily involving the left hemisphere in early AD and MCI patients. The relationship between autobiographical memory, personal semantic memory and autonoetic awareness (studied with the Episodic Autobiographical Memory Interview [EAMI]) with neocortical amyloid beta (Aβ, assessed using amyloid imaging with PET) and Apolipoprotein E (APOE) status has been investigated in a longitudinal study on MCI and AD patients [63]. At the 36-months follow-up visit, authors observed that autobiographical, but not personal semantic memory, could distinguish between MCI and controls. However, AD imaging biomarkers (neocortical Aβ burden), overall GM, hippocampal volumes and APOE status were not associated with autonoetic awareness variables, suggesting that personal memory systems are impacted by different disease mechanisms.

Summary

- Autonoetic awareness is a branch of awareness, and it is defined as the accompanying re-experiencing of an event, and the mental capacity to travel forwards and backwards in time.
- Deficits in episodic autobiographical memory and autonoetic awareness in MCI and AD cases are attributed to morphological changes in the left hippocampus.

Free will

Neuroscientists have tried over the years to study free will and its neural substrates. One key element of free will is being able to voluntarily initiate actions, and choose among a number of potential responses to stimuli generated internally or externally [67]. Therefore, free will can be considered as the direct result of being aware, and specifically being aware of the possibility of choice [68].

Many neuroimaging studies linger on the importance of free will, how it can be explained, and which are its neural correlates. Free will and freedom of choice are highly dependent on intact neurological functioning; therefore certain disturbances associated with specific brain alterations might limit an individual's ability to exercise his/her own free will. Specifically, these aspects are commonly observed in patients with neurodegenerative diseases, especially those belonging to the FTLD spectrum. Structural imaging studies on bvFTD highlighted an involvement of bilateral orbitofrontal, insular and anterior cingulate cortices, as well as of right dorsolateral frontal and left premotor cortices in the free will construct [69]. Particularly, the prefrontal cortex has a crucial role in decoupling perception from action, allowing the individual for internal deliberation and decision-making. When damage to the prefrontal cortex is present, environmental dependency syndrome might occur.

Environmental dependency syndrome: grasping and imitation

This syndrome is a behavioral disorder characterized by the inability to directly control environmental, social, and physical stimuli [70]. Patients with this syndrome exhibit imitation and utilization behaviors, and in both cases the behavioral responses turn out to be inappropriate to the context and do not correspond to their voluntary intention.

A study explored the neural bases of human autonomy and free-will by studying environmental dependency syndrome in bvFTD and PSP patients compared to healthy controls [71]. Authors focused their attention on two main components of environmental dependency syndrome: grasping and imitation behaviors. In the clinical setting, the former can be observed when a patient is asked to hold the examiner's hand after palm stimulation, while the latter corresponds to the spontaneous imitation of the examiner's body or symbolic gestures. Environmental dependency syndrome has been observed to be associated with damage to the frontoparietal network: grasping was found to be associated with GM atrophy of right superior frontal gyrus, while imitation with changes of right insula, left medial frontal gyrus and left precuneus. Furthermore, grasping behavior was more frequent in PSP patients than bvFTD, and was correlated to altered executive functions (tested with the Frontal Assessment Battery and the Wisconsin Card Sorting Test). On the other hand, imitation behavior was not related to executive functioning, and authors emphasized the social nature of the control of imitation, suggesting its relationship with the concepts of agency and self [71].

Metacognition and metamemory

Another aspect linked to the theme of free-will and studied in neurodegenerative diseases is metacognition. Metacognition refers to the human ability to reflect on one's own mental processes, to monitor and control them. Metamemory is one aspect of metacognition, and it is the ability to rebuild memory awareness. A failure to control and manage information stored in memory would lead to a serious lack of decision-making ability due to the unclear picture of the past memory, ultimately compromising the free will. One study [72] explored and measured the neural basis of metamemory capacity in healthy controls and AD, using an objective metamemory test [28]. In both groups, less accurate metamemory was associated with reduced cortical thickness of the right PCC and medial prefrontal cortices.

Delusions

According to a view which states that *'a person is the causal initiator of the action'*, only actions whose source lies in the agent himself can be considered to be free actions [73]. Accordingly, actions performed during altered mental states, such as delusions, might not be considered to stem from the person himself/herself [74]. Among neurodegenerative disorders, about 36% of AD patients may experience delusions, usually manifesting in the persecutory spectrum or misidentification. Delusions are defined as a psychic phenomenon with very different causes, leading to strong alteration of the perception of the outside world, to the point of not distinguishing reality from imagination. The inability to distinguish whether a content is a truthful or falsified perception would therefore entail a lack of objectivity in the patient's choices. A study [75] showed that AD patients with delusions exhibited significant reduction in the intrinsic functional connectivity of the DMN compared with patients without delusions, specifically in the left inferior parietal

lobule. The role of the parietal cortex in delusional states is still not very well documented, but a possible explanation might rely on creating a bridge between the 'self' and 'others' through a process whereby recognition of the actions of others supports self-representation [76].

Summary

- Free will is related to being able to initiate actions, and choose among a number of potential responses to stimuli generated internally or externally.
- BvFTD patients have an involvement of bilateral orbitofrontal, insular and anterior cingulate cortices, and right dorsolateral frontal and left premotor cortices; all these changes are associated with the free will construct.
- Environmental dependency phenomena are associated with dysfunction of the frontoparietal network, and rely on multiple, partially segregated components.
- Grasping and imitation behaviors are two components of environmental dependency syndrome, and are frequently observed in frontal lobe syndromes. Grasping is correlated with volume loss of right superior frontal gyrus and inferior temporal gyri, while imitation with changes of the right insula, left medial frontal gyrus and precuneus.
- Metamemory is an aspect of metacognition, and it is the ability to rebuild memory awareness; less accurate metamemory is associated with reduced cortical thickness in the right PCC and right medial prefrontal regions in both AD patients and controls.
- Delusions cause a strong alteration of the perception of the outside world and, as severity progresses, patient subjectivity is distorted. AD patients with delusions showed significantly reduced intrinsic connectivity within the DMN, specifically in the left inferior parietal lobule.

Discussion

This review discusses the importance of human awareness across specific neurodegenerative diseases belonging to the AD and FTLD *spectra*. "Awareness" is a term still used ambiguously and reflects a complex domain, which contains distinct aspects. Our review faced different constructs of awareness and, for each of them, common and specific structural and functional correlates based on the current MRI literature have been summarized.

Our findings showed that anosognosia occurs in AD since early disease stages [18, 23], mainly reflecting difficulties in evaluating one's own capacities [4, 19]. Several studies observed that anosognosia is secondary to memory deficits in AD and MCI cases and it is associated with mesial temporal alterations, in particular hippocampal damage [26, 27, 39]. Specifically, these populations under- or overestimate their abilities in those daily living activities which heavily rely on memory functioning (e.g., using the phone appropriately, remembering the steps to prepare meals or writing shopping lists) [72]. In relation to this aspect, we also mentioned the possible occurrence of hypernosognosia for memory deficits in preclinical AD; to date, neuroanatomical evidence on the topic is still lacking [13]. We also observed that unawareness of impaired abilities in aMCI patients might be the result of both functional metabolic changes and functional disconnection between regions supporting memory and self-referential processing [27]. The progression of these symptoms, in fact, is associated with the degeneration of dorsal frontal regions, involved in reflecting upon one's behavior in order to align it to long-term goals, as well as orbitofrontal [27] and subcortical regions [4] involved in self-reflection and metacognition [72]. Interestingly, in MCI converters and AD patients, we also retrieved an association between anosognosia and reduced GM volume of the cerebellar vermis [18], which is functionally linked to cortical midline structures and known to have a role in the processing of emotional aspects of information about the self [16]. Recently, increasing attention has been paid also to anosognosia for non-amnestic deficits in AD cohorts, and we observed that the identification of anosognosia for executive problems might help clinicians to discriminate between patients with or without dementia [12]. Unfortunately, our search did not retrieve neuroanatomical studies on this very interesting topic.

Although these terms are often used interchangeably, anosognosia and lack of insight do not reflect the same construct. In fact, insight impairment includes the attitude of being detached about the consequences of a proper action or behavior [77]. Rather than anosognosia for cognitive deficits (as in AD and MCI cases), it is the lack of insight that characterizes the bvFTD disorder [34]. Specifically, loss of social and emotional aspects of insight (such as inappropriate behavior and disinhibition in social interactions) is frequent in these patients and it is among the core features for the clinical diagnosis of bvFTD [78]. In bvFTD, overall insight loss has been consistently found in relation to ventromedial and frontopolar prefrontal alterations, while specific insight deficits during social interaction have been linked to atrophy of lateral temporal regions and lateral amygdala [35]. We observed that bvFTD patients have the most severe insight problems related to social interaction, motivation and emotion compared to AD and other FTLD-related disorders; thus, the atrophy pattern that we reported specifically associated to insight deficits during social interaction could be considered a marker useful to predict the degree of insight loss in these patients. Our review further underlines that social cognition impairment, as a variety of processes which enable human beings to interact with their peers and be aware

of their intentions and thoughts, reflects primary deficits in FTLD [47], are more frequent than in AD, and are not specific to bvFTD only but can be observed in other FTLD disorders, such as PPA [44, 47, 57, 62], ALS, PSP [25, 41, 46, 71] and CBS [44, 46]. However, the studies included in the present review did not specifically provide exhaustive findings on less common diseases, such as PPA, PSP, LBD and CBS. The few studies reporting data on these rare disorders included only a scarce number of participants, and did not provide further information on differences among these distinct clinical syndromes. Therefore, future studies on awareness and targeting these less common syndromes are needed.

Here we highlighted the importance of the SN in socioemotional functioning of FTLD [55]: the disruption of regions pertaining to this network (e.g., anterior insular cortices and ACC) [52] in FTLD populations is often linked to emotional reactivity and to the inability of these patients to analyze internal and others' emotional states, therefore misinterpreting social situations and consequently demonstrating impulsive behavioral responses [40, 41]. This decreased emotional concern for the consequences of their acts is related to the so-called FTLD "sociopathy", which is subtended by a lack in impulse control: these patients might display even early in their disease course a loss of social propriety, inappropriate physical contact and interactions with others, improper thoughts and communication with interlocutors, unsolicited sexual acts, traffic violations, or acts of violence [79]. FTLD patients have a 'factual awareness' of their behavior (they know what is right and wrong and the consequences of their actions), but they lack emotional awareness. Given their tendency to 'sociopathy', FTLD patients might commit crimes and therefore can be arrested: this raises the issues of legal culpability and fair trials for these patients [80].

We observed that social cognition in FTLD is further subtended by a distributed network involving also orbitofrontal, lateral temporal cortex, amygdala and temporoparietal junction, which are regions mainly linked to both affective and cognitive ToM [81]. All these behavioral problems are key elements that can help distinguishing AD from FTLD cases since the earliest stages of the disease.

In AD, beyond anosognosia, other affected aspects related to awareness, such as impairment in autonoetic awareness, metamemory, ToM and moral reasoning, are secondary to difficulties in retrieving and monitoring autobiographical experiences and/or recent episodic events, and again linked to mesial temporal dysfunction, particularly hippocampal, and PCC involvement [39, 72]. As such, these patients lose the advantage to draw from their past experiences the knowledge previously learned and to re-use it in more favorable ways for decision-making or intention understanding of others.

On a related note, our review also focused on the open debate about free will. We focused on behavioral aspects of this domain as a consequence of a disruption of frontal lobe circuits and mainly occurring in bvFTD since the early stages. Such aspects are environmental dependency syndrome [70], grasping and imitation behaviors [71], which posits the problem (still unsolved) of the existence of human autonomy and free decision-making.

Also, the presence of delusions in AD cases, which reflects the inability to distinguish reality from distorted perception, leads to a lack of objectivity in the patient's choices. Furthermore, in delusional states, individuals impose their own explanation in interpreting their experience, rather than applying logical reasoning mediated by sensory information [82]. In AD, these disturbances are often associated with a reduced functional connectivity of the inferior parietal lobe within the DMN [75], as this region is known to provide a stable egocentric reference frame for the representation of the self in healthy individuals [76]. During delusional states, individuals can perform wrongful actions ending up in legal consequences: this issue raises alertness on the wide topic of the ethics of belief and on the concept of "innocence defense". This defense applies when an harmful act is not considered as wrongful by the actor of the action, which might be the case of our patients [83].

Some limitations of the present review should be noted. Although the research string was built to be as comprehensive as possible, the selected studies might only partially reflect the huge available scientific literature in the field, since our manuscript did not review literature on other imaging techniques than MRI. We included only a few studies which combined MRI and molecular imaging [18, 24, 27, 29, 32, 63], but MRI was always the primary method of investigation. Furthermore, due to the rarity of some neurological disorders debated in this review, some of the included studies regarded only small cohorts of patients (less than ten patients per group), thus reducing the generalization of the reported findings. Finally, only a few selected studies targeted less common FTLD diseases, such as PPA variants [4, 35, 41, 42, 44, 46, 47, 62], PSP [41, 46, 71] and CBS [44, 46]. Unfortunately, our search string did not retrieve studies on ALS disorder. Further works are therefore needed to investigate awareness problems in these cohorts.

Despite these limitations, the present manuscript has a few strengths. Firstly, we performed a formal literature search using a robust methodological approach, and we reviewed the obtained scientific papers through a double-blinded screening approach, which was conducted by two independent reviewers. Second, the present work provides a state-of-the-art summary of recent findings on the topic of awareness impairment across several neurodegenerative disorders belonging to the AD and FTLD *spectra*. Lastly, the present findings stress out the importance of using MRI

to support behavioral findings and better characterize the patients with the use of early biomarkers.

Conclusions

The purpose of this review was to investigate the neural correlates that underlie the lack of awareness of AD and FTLD *spectra* of disorders. In the results, we analyzed the different constructs of awareness alterations, with an effort in outlining how MRI can explain these dysfunctions through the associations with specific patterns of structural and functional impairment in the main neurodegenerative disorders. In brief, we characterized and distinguish the different constructs of awareness, which is a complex domain consisting in multiple aspects, both from a theoretical and neuroimaging point of view. Loss of awareness in AD and FTLD populations has been mainly associated with brain alterations both at structural and functional level of midline cortical structures, and of fronto-striatal, fronto-parietal, and limbic circuits. However, some of the aspects relative to awareness impairment are affected at different stages of AD and bvFTD and are subtended by either common or distinct brain circuits. Future studies should also investigate the neural correlates of anosognosia for non-amnestic complaints, and to further study the hypothetical continuum ranging from normal awareness of cognitive impairment, hypernosognosia and full anosognosia in neurodegenerative disorders. To conclude, we highlighted the importance of awareness alterations and related disturbances in neurodegenerative disorders, and we provided a general overview of their structural and functional correlates.

Funding This work was supported by the European Research Council [Grant Number: StG2016_714388_NeuroTRACK] and the Foundation Research on Alzheimer Disease.

Data availability This study is a review of already published data.

Declarations

Conflicts of interest M. Leocadi and A. Paldino report no disclosures. E. Canu has received research supports from the Italian Ministry of Health. F. Agosta is Associate Editor of *NeuroImage: Clinical*, has received speaker honoraria from Roche and Biogen Idec, and receives or has received research supports from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), and the European Research Council. M. Filippi is Editor-in-Chief of the *Journal of Neurology*, Associate Editor of *Human Brain Mapping*, Associate Editor of *Radiology*, and Associate Editor of *Neurological Sciences*; received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Neopharmed Gentili, Novartis, Roche, Sanofi, Takeda, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Ethical approval The manuscript does not contain clinical studies or patient data.

Consent The manuscript does not contain clinical studies or patient data.

References

1. Stuss DT, Anderson V (2004) The frontal lobes and theory of mind: developmental concepts from adult focal lesion research. Brain Cogn 55:69–83
2. Kotchoubey B (2018) Human consciousness: where is it from and what is it for. Front Psychol 9:567
3. Flashman LA (2002) Disorders of awareness in neuropsychiatric syndromes: an update. Curr Psychiatry Rep 4:346–353
4. Shany-Ur T, Lin N, Rosen HJ, Sollberger M, Miller BL, Rankin KP (2014) Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. Brain 137:2368–2381
5. Sunderaraman P, Cosentino S (2017) Integrating the constructs of anosognosia and metacognition: a review of recent findings in dementia. Curr Neurol Neurosci Rep 17:27
6. Chavoix C, Insausti R (2017) Self-awareness and the medial temporal lobe in neurodegenerative diseases. Neurosci Biobehav Rev 78:1–12
7. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J (2006) Self-referential processing in our brain–a meta-analysis of imaging studies on the self. Neuroimage 31:440–457
8. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. Syst Rev 5:210
9. Ansell EL, Bucks RS (2006) Mnemonic anosognosia in Alzheimer's disease: a test of Agnew and Morris (1998). Neuropsychologia 44:1095–1102
10. Tabert MH, Albert SM, Borukhova-Milov L, Camacho Y, Pelton G, Liu X, Stern Y, Devanand DP (2002) Functional deficits in patients with mild cognitive impairment: prediction of AD. Neurology 58:758–764
11. Montembeault M, Stijelja S, Brambati SM, Alzheimer's Disease Neuroimaging I (2022) Self-reported word-finding complaints are associated with cerebrospinal fluid amyloid beta and atrophy in cognitively normal older adults. Alzheimers Dement (Amst) 14:e12274
12. Cacciamani F, Godefroy V, Brambati SM, Migliaccio R, Epelbaum S, Montembeault M (2022) Differential patterns of domain-specific cognitive complaints and awareness across the Alzheimer's disease spectrum. Front Aging Neurosci 14:811739
13. Vannini P, Amariglio R, Hanseeuw B, Johnson KA, McLaren DG, Chhatwal J, Pascual-Leone A, Rentz D, Sperling RA (2017) Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. Neuropsychologia 99:343–349
14. Cacciamani F, Houot M, Gagliardi G, Dubois B, Sikkes S, Sanchez-Benavides G, Denicolo E, Molinuevo JL, Vannini P, Epelbaum S (2021) Awareness of cognitive decline in patients with Alzheimer's disease: a systematic review and meta-analysis. Front Aging Neurosci 13:697234
15. Ford AH, Almeida OP, Flicker L, Garrido GJ, Greenop KR, Foster JK, Etherton-Beer C, van Bockxmeer FM, Lautenschlager NT (2014) Grey matter changes associated with deficit awareness in mild cognitive impairment: a voxel-based morphometry study. J Alzheimers Dis 42:1251–1259

16. Spalletta G, Piras F, Piras F, Sancesario G, Iorio M, Fratangeli C, Cacciari C, Caltagirone C, Orfei MD (2014) Neuroanatomical correlates of awareness of illness in patients with amnestic mild cognitive impairment who will or will not convert to Alzheimer's disease. Cortex 61:183–195
17. Senturk G, Bilgic B, Arslan AB, Bayram A, Hanagasi H, Gurvit H, Emre M (2017) Cognitive and anatomical correlates of anosognosia in amnestic mild cognitive impairment and early-stage Alzheimer's disease. Int Psychogeriatr 29:293–302
18. Guerrier L, Le Men J, Gane A, Planton M, Salabert AS, Payoux P, Dumas H, Bonneville F, Peran P, Pariente J (2018) Involvement of the cingulate cortex in anosognosia: a multimodal neuroimaging study in Alzheimer's disease patients. J Alzheimers Dis 65:443–453
19. Steward KA, Kennedy R, Erus G, Nasrallah IM, Wadley VG (2019) Poor awareness of IADL deficits is associated with reduced regional brain volume in older adults with cognitive impairment. Neuropsychologia 129:372–378
20. Ries ML, Jabbar BM, Schmitz TW, Trivedi MA, Gleason CE, Carlsson CM, Rowley HA, Asthana S, Johnson SC (2007) Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. J Int Neuropsychol Soc 13:450–461
21. Ries ML, McLaren DG, Bendlin BB, Guofanxu RHA, Birn R, Kastman EK, Sager MA, Asthana S, Johnson SC (2012) Medial prefrontal functional connectivity–relation to memory self-appraisal accuracy in older adults with and without memory disorders. Neuropsychologia 50:603–611
22. Zamboni G, Drazich E, McCulloch E, Filippini N, Mackay CE, Jenkinson M, Tracey I, Wilcock GK (2013) Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. Cortex 49:668–678
23. Amanzio M, Torta DM, Sacco K, Cauda F, D'Agata F, Duca S, Leotta D, Palermo S, Geminiani GC (2011) Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. Brain 134:1061–1076
24. Amanzio M, D'Agata F, Palermo S, Rubino E, Zucca M, Galati A, Pinessi L, Castellano G, Rainero I (2016) Neural correlates of reduced awareness in instrumental activities of daily living in frontotemporal dementia. Exp Gerontol 83:158–164
25. McGlynn SM, Schacter DL (1989) Unawareness of deficits in neuropsychological syndromes. J Clin Exp Neuropsychol 11:143–205
26. Sanchez-Benavides G, Grau-Rivera O, Cacciaglia R, Suarez-Calvet M, Falcon C, Minguillon C, Gramunt N, Sala-Vila A, Gispert JD, Molinuevo JL (2018) Distinct cognitive and brain morphological features in healthy subjects unaware of informant-reported cognitive decline. J Alzheimers Dis 65:181–191
27. Vannini P, Hanseeuw B, Munro CE, Amariglio RE, Marshall GA, Rentz DM, Pascual-Leone A, Johnson KA, Sperling RA (2017) Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. Neuroimage Clin 15:408–414
28. Cosentino S, Brickman AM, Griffith E, Habeck C, Cines S, Farrell M, Shaked D, Huey ED, Briner T, Stern Y (2015) The right insula contributes to memory awareness in cognitively diverse older adults. Neuropsychologia 75:163–169
29. Perrotin A, Desgranges B, Landeau B, Mezenge F, La Joie R, Egret S, Pelerin A, de la Sayette V, Eustache F, Chetelat G (2015) Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. Ann Neurol 78:477–486
30. Antoine N, Bahri MA, Bastin C, Collette F, Phillips C, Balteau E, Genon S, Salmon E (2019) Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. Hum Brain Mapp 40:5330–5340
31. Crutch SJ, Schott JM, Rabinovici GD, Murray M, Snowden JS, van der Flier WM, Dickerson BC, Vandenberghe R, Ahmed S, Bak TH, Boeve BF, Butler C, Cappa SF, Ceccaldi M, de Souza LC, Dubois B, Felician O, Galasko D, Graff-Radford J, Graff-Radford NR, Hof PR, Krolak-Salmon P, Lehmann M, Magnin E, Mendez MF, Nestor PJ, Onyike CU, Pelak VS, Pijnenburg Y, Primativo S, Rossor MN, Ryan NS, Scheltens P, Shakespeare TJ, Gonzalez AS, Tang-Wai DF, Yong KXX, Carrillo M, Fox NC, AsAI A (2017) Consensus classification of posterior cortical atrophy. Alzheimers Dement 13:870–884
32. Mendez MF, Ghajarania M, Perryman KM (2002) Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. Dement Geriatr Cogn Disord 14:33–40
33. Marková IS, Berrios GE (2011) Awareness and insight in psychopathology: An essential distinction? Theory Psychol 21:421–437
34. Eslinger P, Dennis K, Moore P, Antani S, Hauck R, Grossman M (2005) Metacognitive deficits in frontotemporal dementia. J Neurol Neurosurg Psychiatry 76:1630–1635
35. Hornberger M, Yew B, Gilardoni S, Mioshi E, Gleichgerrcht E, Manes F, Hodges JR (2014) Ventromedial-frontopolar prefrontal cortex atrophy correlates with insight loss in frontotemporal dementia and Alzheimer's disease. Hum Brain Mapp 35:616–626
36. Magno MA, Canu E, Agosta F, Filippi M (2022) Measuring social cognition in frontotemporal lobar degeneration: a clinical approach. J Neurol 269:2227–2244
37. Belfort T, Simoes P, de Sousa MFB, Santos RL, Barbeito I, Torres B, Dourado MCN (2018) The relationship between social cognition and awareness in Alzheimer disease. J Geriatr Psychiatry Neurol 31:27–33
38. Giovagnoli AR, Bell B, Erbetta A, Paterlini C, Bugiani O (2019) Analyzing theory of mind impairment in patients with behavioral variant frontotemporal dementia. Neurol Sci 40:1893–1900
39. Synn A, Mothakunnel A, Kumfor F, Chen Y, Piguet O, Hodges JR, Irish M (2018) Mental states in moving shapes: distinct cortical and subcortical contributions to theory of mind impairments in dementia. J Alzheimers Dis 61:521–535
40. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356
41. Toller G, Brown J, Sollberger M, Shdo SM, Bouvet L, Sukhanov P, Seeley WW, Miller BL, Rankin KP (2018) Individual differences in socioemotional sensitivity are an index of salience network function. Cortex 103:211–223
42. Shinagawa S, Babu A, Sturm V, Shany-Ur T, Toofanian Ross P, Zackey D, Poorzand P, Grossman S, Miller BL, Rankin KP (2015) Neural basis of motivational approach and withdrawal behaviors in neurodegenerative disease. Brain Behav 5:e00350
43. Kalbe E, Salmon E, Perani D, Holthoff V, Sorbi S, Elsner A, Weisenbach S, Brand M, Lenz O, Kessler J, Luedecke S, Ortelli P, Herholz K (2005) Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. Dement Geriatr Cogn Disord 19:349–356
44. Sollberger M, Rosen HJ, Shany-Ur T, Ullah J, Stanley CM, Laluz V, Weiner MW, Wilson SM, Miller BL, Rankin KP (2014) Neural substrates of socioemotional self-awareness in neurodegenerative disease. Brain Behav 4:201–214
45. Jastorff J, De Winter FL, Van den Stock J, Vandenberghe R, Giese MA, Vandenbulcke M (2016) Functional dissociation between anterior temporal lobe and inferior frontal gyrus in the processing of dynamic body expressions: insights from behavioral variant frontotemporal dementia. Hum Brain Mapp 37:4472–4486
46. Reus LM, Vijverberg EG, Tijms BM, Kate MT, Gossink F, Krudop WA, Campo MD, Teunissen CE, Barkhof F, van der Flier WM, Visser PJ, Dols A, Pijnenburg YA (2018) Disease trajectories in behavioural variant frontotemporal dementia, primary

psychiatric and other neurodegenerative disorders presenting with behavioural change. J Psychiatr Res 104:183–191
47. Hutchings R, Hodges JR, Piguet O, Kumfor F, Boutoleau-Bretonniere C (2015) Why should I care? Dimensions of socio-emotional cognition in younger-onset dementia. J Alzheimers Dis 48:135–147
48. Moll J, Zahn R, de Oliveira-Souza R, Bramati IE, Krueger F, Tura B, Cavanagh AL, Grafman J (2011) Impairment of prosocial sentiments is associated with frontopolar and septal damage in frontotemporal dementia. Neuroimage 54:1735–1742
49. Shearn D, Bergman E, Hill K, Abel A, Hinds L (1990) Facial coloration and temperature responses in blushing. Psychophysiology 27:687–693
50. Sturm VE, Ascher EA, Miller BL, Levenson RW (2008) Diminished self-conscious emotional responding in frontotemporal lobar degeneration patients. Emotion 8:861–869
51. Sturm VE, Rosen HJ, Allison S, Miller BL, Levenson RW (2006) Self-conscious emotion deficits in frontotemporal lobar degeneration. Brain 129:2508–2516
52. Sturm VE, Sollberger M, Seeley WW, Rankin KP, Ascher EA, Rosen HJ, Miller BL, Levenson RW (2013) Role of right pregenual anterior cingulate cortex in self-conscious emotional reactivity. Soc Cogn Affect Neurosci 8:468–474
53. Kuilman L, Jansen GJ, Middel B, Mulder LB, Roodbol PF (2019) Moral reasoning explained by personality traits and moral disengagement: a study among Dutch nurse practitioners and physician assistants. J Adv Nurs 75:1252–1262
54. Shany-Ur T, Rankin KP (2011) Personality and social cognition in neurodegenerative disease. Curr Opin Neurol 24:550–555
55. Chiong W, Wilson SM, D'Esposito M, Kayser AS, Grossman SN, Poorzand P, Seeley WW, Miller BL, Rankin KP (2013) The salience network causally influences default mode network activity during moral reasoning. Brain 136:1929–1941
56. Wong S, Irish M, O'Callaghan C, Kumfor F, Savage G, Hodges JR, Piguet O, Hornberger M (2017) Should I trust you? Learning and memory of social interactions in dementia. Neuropsychologia 104:157–167
57. Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR (2009) Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. Brain 132:592–603
58. Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC (2015) Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 43:1271–1284
59. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO (1989) Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 262:2551–2556
60. Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194
61. Mesulam M, Shaw P, Mash D, Weintraub S (2004) Cholinergic nucleus basalis tauopathy emerges early in the aging-MCI-AD continuum. Ann Neurol 55:815–828
62. Downey LE, Mahoney CJ, Buckley AH, Golden HL, Henley SM, Schmitz N, Schott JM, Simpson IJ, Ourselin S, Fox NC, Crutch SJ, Warren JD (2015) White matter tract signatures of impaired social cognition in frontotemporal lobar degeneration. NeuroImage Clinical 8:640–651
63. Buckley RF, Saling MM, Irish M, Ames D, Rowe CC, Villemagne VL, Lautenschlager NT, Maruff P, Macaulay SL, Martins RN, Szoeke C, Masters CL, Rainey-Smith SR, Rembach A, Savage G, Ellis KA, Australian Imaging B, Lifestyle Study of Ageing Research G (2014) Autobiographical narratives relate to Alzheimer's disease biomarkers in older adults. Int Psychogeriatr 26:1737–1746
64. Bozeat S, Gregory CA, Ralph MA, Hodges JR (2000) Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 69:178–186
65. Robinson JA, Swanson KL (1990) Autobiographical memory: the next phase. Appl Cogn Psychol 4:321–335
66. Thomann PA, Seidl U, Brinkmann J, Hirjak D, Traeger T, Wolf RC, Essig M, Schroder J (2012) Hippocampal morphology and autobiographic memory in mild cognitive impairment and Alzheimer's disease. Curr Alzheimer Res 9:507–515
67. Drubach DA, Rabinstein AA, Molano J (2011) Free will, freedom of choice and frontotemporal lobar degeneration. Mens Sana Monographs 9:238
68. Gomes G (2007) Free will, the self, and the brain. Behav Sci Law 25:221–234
69. Rosen HJ, Gorno-Tempini ML, Goldman W, Perry R, Schuff N, Weiner M, Feiwell R, Kramer J, Miller BL (2002) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 58:198–208
70. Lhermitte F, Pillon B, Serdaru M (1986) Human autonomy and the frontal lobes. Part I: imitation and utilization behavior: a neuropsychological study of 75 patients. Ann Neurol 19:326–334
71. Lagarde J, Valabregue R, Corvol JC, Le Ber I, Colliot O, Vidailhet M, Levy R (2013) The clinical and anatomical heterogeneity of environmental dependency phenomena. J Neurol 260:2262–2270
72. Bertrand E, Azar M, Rizvi B, Brickman AM, Huey ED, Habeck C, Landeira-Fernandez J, Mograbi DC, Cosentino S (2018) Cortical thickness and metacognition in cognitively diverse older adults. Neuropsychology 32:700–710
73. Widerker D (2017) Moral responsibility and alternative possibilities: essays on the importance of alternative possibilities. Routledge
74. Meynen G (2010) Free will and mental disorder: exploring the relationship. Theor Med Bioeth 31:429–443
75. Qian W, Fischer CE, Churchill NW, Kumar S, Rajji T, Schweizer TA (2019) Delusions in Alzheimer disease are associated with decreased default mode network functional connectivity. Am J Geriatr Psychiatry 27:1060–1068
76. Guo SX, Kendrick KM, Yu RJ, Wang HLS, Feng JF (2014) Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. Hum Brain Mapp 35:123–139
77. Zanetti O, Vallotti B, Frisoni GB, Geroldi C, Bianchetti A, Pasqualetti P, Trabucchi M (1999) Insight in dementia: When does it occur? Evidence for a nonlinear relationship between insight and cognitive status. J Gerontol B-Psychol 54:P100–P106
78. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134:2456–2477
79. Mendez MF, Anderson E, Shapira JS (2005) An investigation of moral judgement in frontotemporal dementia. Cogn Behav Neurol 18:193–197
80. Mendez MF, Chen AK, Shapira JS, Miller BL (2005) Acquired sociopathy and frontotemporal dementia. Dement Geriatr Cogn Disord 20:99–104

81. Magno MA, Canu E, Filippi M, Agosta F (2022) Social cognition in the FTLD spectrum: evidence from MRI. J Neurol 269:2245–2258
82. Schilbach L, Eickhoff SB, Rska-Jagiela AR, Fink GR, Vogeley K (2008) Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious Cogn 17:457–467
83. Bortolotti L, Miyazono K (2016) The ethics of delusional belief. Erkenntnis 81:275–296
84. Jorm AF, Jacomb PA (1989) The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 19:1015–1022
85. Migliorelli R, Teson A, Sabe L, Petracca G, Petracchi M, Leiguarda R, Starkstein SE (1995) Anosognosia in Alzheimer's disease: a study of associated factors. J Neuropsychiatry Clin Neurosci 7:338–344
86. Clare L, Markova IS, Roth I, Morris RG (2011) Awareness in Alzheimer's disease and associated dementias: theoretical framework and clinical implications. Aging Ment Health 15:936–944
87. Anderson NH (1968) Likableness ratings of 555 personality-trait words. J Pers Soc Psychol 9:272–279
88. Prigatano GP (1996) Neuropsychological rehabilitation after brain injury: Scientific and professional issues. J Clin Psychol Med Settings 3:1–10
89. Browne GB, Byrne C, Roberts J, Streiner D, Fitch M, Corey P, Arpin K (1988) The meaning of illness questionnaire: reliability and validity. Nurs Res 37:368–373
90. Irak M, Soylu C, Turan G, Capan D (2019) Neurobiological basis of feeling of knowing in episodic memory. Cogn Neurodyn 13:239–256
91. Ott BR, Lafleche G, Whelihan WM, Buongiorno GW, Albert MS, Fogel BS (1996) Impaired awareness of deficits in Alzheimer disease. Alzheimer Dis Assoc Disord 10:68–76
92. Gass CS, Patten B, Penate A, Rhodes A (2021) The Cognitive Difficulties Scale (CDS): psychometric characteristics in a clinical referral sample. J Int Neuropsychol Soc 27:351–364
93. Wear HJ, Wedderburn CJ, Mioshi E, Williams-Gray CH, Mason SL, Barker RA, Hodges JR (2008) The Cambridge Behavioural Inventory revised. Dement Neuropsychol 2:102–107
94. Davis MH (1983) Measuring individual differences in empathy: evidence for a multidimensional approach. J Pers Soc Psychol 44:113
95. White SJ, Coniston D, Rogers R, Frith U (2011) Developing the Frith-Happe animations: a quick and objective test of Theory of Mind for adults with autism. Autism Res 4:149–154
96. Stone VE, Baron-Cohen S, Knight RT (1998) Frontal lobe contributions to theory of mind. J Cogn Neurosci 10:640–656
97. McDonald S, Flanagan S, Rollins J, Kinch J (2003) TASIT: a new clinical tool for assessing social perception after traumatic brain injury. J Head Trauma Rehabil 18:219–238
98. Carver CS, White TL (1994) Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol 67:319
99. Bramham J, Morris RG, Hornak J, Bullock P, Polkey CE (2009) Social and emotional functioning following bilateral and unilateral neurosurgical prefrontal cortex lesions. J Neuropsychol 3:125–143
100. Lennox RD, Wolfe RN (1984) Revision of the self-monitoring scale. J Pers Soc Psychol 46:1349–1364
101. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2308