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REVIEW ARTICLE

Neural correlates of apathy in patients with neurodegenerative disorders: an activation likelihood estimation (ALE) meta-analysis

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Abstract

Apathy is commonly reported in Alzheimer's Disease (AD), Fronto-Temporal Dementia (FTD) and Parkinson's Disease (PD). In our meta-analysis we analysed a total of 41 studies to identify brain patterns associated with apathy. For these purposes we used activation likelihood estimation meta-analyses. Our main overall analysis showed that apathy is associated to hypometabolism and a decreased gray matter volume in the left inferior frontal gyrus (BA 45, 46). Disorder-specific analyses, not performed by means of meta-analysis, because of the small number of studies, but by means a label-based review, revealed an altered brain perfusion and decreased gray matter volume in anterior cingulate cortex (BA 24, 32) in AD patients and a decreased gray matter volume in inferior frontal gyrus (BA 44, 45) and parietal cortex (BA 40) in FTD patients. These findings suggest that apathy is mainly associated with a cortical dysfunction of areas involved in executive-cognitive processing (i.e. action planning) and emotional regulation (auto-activation and reward processing). Knowledge about the neural underpinnings of apathy is crucial for understanding its clinical characteristics in neurodegenerative diseases and for developing novel strategies of treatment in clinical practice.

Keywords Apathy · Neural correlates · Meta-analysis · Alzheimer disease · Dementia · Parkinson disease

Introduction

Apathy is a behavioral syndrome encompassing a set of behavioral, affective and cognitive features (Marin 1991). Apathy can be defined as a state of decreased motivation variably characterised by loss of goal-directed behaviors and reduced interests or emotions, that cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress (Marin 1991; Levy and Dubois 2006). The construct of apathy can be divided into three subtypes: cognitive apathy would be characterized by difficulties in elaborating action plans necessary for ongoing or forthcoming behaviour; behavioural apathy would correspond to the inability to self-activate thoughts or self-initiate actions in presence of a relatively spared ability to generate externally driven behaviour; emotional apathy would consist in the inability to establish the necessary linkage between emotional–affective signals and ongoing or forthcoming behaviour (Levy and Dubois 2006).

According to recent international consensus criteria apathy is defined as a syndrome of diminished motivation persistent over time, that includes symptoms on at least two of the above dimensions (loss of goal-directed behaviour, loss of goal-directed cognitive processing, loss of emotions; Robert et al. 2009).

Apathy has been observed in several neurological disorders, such as Parkinson's disease (PD, Starkstein et al. 1992), Alzheimer's disease (AD, van Reekum et al. 2005) and other dementias (Eslinger et al. 2012), it is correlated with relevant functional disability (Pedersen et al. 2009), huge burden and stress in patients' caregivers (Landes et al. 2001).

Apathy is highly frequent in AD (60%, Clarke et al. 2011), fronto-temporal dementia (FTD, 60%–90%, Levy et al. 1996;

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Chow 2005; 2009) and PD (35%, Santangelo et al. 2013). Early studies investigating the neural bases of apathy in AD by Single Photon Emission Computed Tomography (SPECT) found that apathy was associated with decreased right temporo-parietal perfusion (Ott et al. 1996) or severe prefrontal and anterior temporal dysfunction (Craig et al. 1996). Later SPECT studies (i.e., Migneco et al. 2001; Benoit et al. 2002) showed that AD patients with apathy had significantly decreased perfusion in the left anterior cingulate, the right inferior and medial frontal gyrus, the left orbitofrontal gyrus and the right lingualis gyrus with respect to healthy individuals; moreover, apathetic patients with or without dementia had a significant hypoperfusion in anterior cingulate cortex with respect to non-apathetic individuals.

One study considering emotional, cognitive and behavioural dimensions of apathy separately (as suggested by Marin 1991) reported that lack of initiative correlated with reduced perfusion in right anterior cingulate cortex, lack of interest correlated with hypoperfusion in right middle orbitofrontal gyrus, emotional blunting correlated with hypoperfusion in left superior dorsolateral prefrontal cortex (Benoit et al. 2015). Robert et al. (2006), instead, found that lack of initiative and interest correlated with altered perfusion in the right prefrontal (Brodmann Area, BA 10) and the right inferior temporal lobes; the direct comparison between AD patients with or without lack of initiative and interest showed a significantly lower perfusion in the right anterior cingulate in apathetic patients, suggesting that motivational aspects of apathy rather than emotional aspects would be related to dysfunction of the cingulate area.

From this brief overview, several inconsistencies emerge about neural dysfunctions associated to apathy in AD, even when taking into account the different dimensions of apathy. One important factor contributing to heterogeneity of findings about the neural bases of apathy in AD could be related to association with other disturbances, such as depression, that are often comorbid with and share part of their symptomatology with apathy (Levy et al. 1998). Indeed, when depression and apathy coexist (Benoit 2015; Robert et al. 2006), both a decrease of functional connectivity of the salience network (anterior insula and dorsal anterior cingulate), an increase of functional connectivity of the central executive control (dorsolateral prefrontal cortex and posterior parietal cortex) and of the default-mode network (posterior cingulate and ventromedial prefrontal cortex) have been reported. Studies addressing depression only often report a pattern of increased functional connectivity in the default-mode network (Yuen et al. 2014).

Studies excluding depressed AD patients (Holthoff et al. 2005; Lanctôt et al. 2007) or considering depressed mood as a covariate (Marshall et al. 2007) reported that AD patients with apathy had lower perfusion in orbitofrontal cortex and anterior cingulate cortex than AD patients without apathy, confirming the distinction between regional brain correlates of apathy and depression, suggesting that neurobiological correlates of apathy in AD are independent from those involved in depressed mood.

Moreover, other factors could have contributed to heterogeneity of findings, such as inclusion of small samples, often not controlled for general levels of disease severity, different assessment methods and different types of analysis (i.e., correlations/comparisons between apathetic patients and not apathetic patients/comparisons between apathetic patients and healthy controls).

Magnetic resonance imaging (MRI) studies too provided relatively divergent conclusions, since some of them reported a strong association between apathy and atrophy of anterior cingulate and medial frontal cortex in AD (Apostolova et al. 2007; Tunnard et al. 2011), whereas others (Bruen et al. 2008; Moon et al. 2014) found significant correlations between apathy and insula and basal ganglia alteration.

In patients with the frontal variant of FTD (fv-FTD) PET studies (Franceschi et al. 2005; Peters et al. 2006) showed that apathy was associated with a prevalent dorsolateral and frontal medial hypometabolism; a SPECT study (Borroni et al. 2012) showed that apathy was associated with a dorsolateral frontal and anterior cingulate cortex hypoperfusion. In addition, neuroanatomical evidence from MRI studies (i.e. Rosen et al. 2005; Zamboni et al. 2008; Massimo et al. 2009) showed that apathy is related with alterations in the anterior cingulate cortex and dorsolateral prefrontal cortex. Later on, voxel-based morphometric studies (i.e. Eslinger et al. 2012; Farb et al. 2013; Day et al. 2013) found that apathy was related to prominent atrophy in several subcortical (the right caudate, including the ventral striatum) and cortical areas (the right temporo-parietal junction, right posterior inferior and middle temporal gyri and left frontal operculum-anterior insula region).

In PD patients with or without major depression a Positron Emission Tomography (PET) study by Remy et al. (2005) showed that apathy was associated to decreased ^{11}C-RTI-32 binding (dopamine and noradrenaline) in ventral striatum bilaterally. In another PET study performed after deep brain stimulation of the subthalamic nucleus (Le Jeune et al. 2009), apathy was significantly correlated with decreased glucose metabolism in the left middle frontal gyrus and in the bilateral posterior cingulate gyrus, with increased metabolic activity in the right frontal lobe, postcentral gyrus and temporal lobe. A more recent PET study (Robert et al. 2012) found that metabolism within bilateral posterior lobe of the cerebellum inversely correlated with apathy severity, supporting the view of a topographic functional segmentation of the cerebellum. Bilateral atrophy of posterior cerebellar lobe was found in a MRI study by Skidmore et al. (2013), who also reported a correlation of apathy with atrophy of the left supplementary motor cortex, the right orbitofrontal cortex and the right middle frontal cortex. According to Skidmore et al. (2013)

these data suggest that in PD patients apathy related to orbitofrontal lobe dysfunction might be an "active-avoidant" syndrome, whereas apathy related to motor areas dysfunction might be a purely "amotivational" syndrome. Consistent with the suggestion that apathy in PD might represent an "amotivational" syndrome due to an "autoactivation" deficit, Reijnders et al. (2010) found that apathy was significantly correlated with low gray matter density values in bilateral precentral gyrus, bilateral inferior parietal gyrus, bilateral inferior frontal gyrus, bilateral insula, right posterior cingulate gyrus and right precuneus.

A recent systematic review on the neural correlates of apathy in patients with neurodegenerative disorders (Kos et al. 2016) included only studies including patients with PD, FTD or AD due to the low number of studies addressing this issue in other neurodegenerative disorders (e.g. Levy Body Disease and vascular dementia). Kos et al. (2016) reported a consistent association between apathy and abnormalities within fronto-striatal circuits involving anterior cingulate cortex and inferior parietal cortex. However, the authors suggested the relevance to perform a quantitative analysis that could provide deeper insight on neural basis of apathy in these neurodegenerative disorders (AD, FTD and PD). Therefore, we performed an activation likelihood estimation (ALE) meta-analysis to explore shared and disease-specific brain areas associated with apathy in neurodegenerative disorders in which it was most frequently reported and investigated.

Materials and methods

Data source

A systematic selection of appropriate peer-reviewed studies was undertaken by searching the databases of PubMed, SciVerse Scopus, Web of Science and by checking references cited in each paper (July, 2018). The keyword combination "apath*" AND "neuroimaging" OR "magnetic resonance imaging" OR "MRI" OR "functional magnetic resonance" OR "fMRI" OR "positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" AND "Parkinson" OR "Dementia". Search terms and total of articles found are shown in supplemental material 1.

Selection criteria

The process of selecting eligible articles was performed according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Moher et al. 2009). The flow chart of the selection process is shown in Fig. 1. Only studies that met the following inclusion criteria were considered for analysis: i) original data were presented (thus, review papers were excluded but their references were manually reviewed for inclusion of additional publications that might have been missed during the data search), ii) study was conducted with human participants, iii) study with clinical samples including only patients diagnosed with AD, FTD or PD, iv) methods included brain imaging techniques described as keywords above; v) whole-brain analysis was conducted (excluding studies reporting only region of interest ROI analysis or seed based analysis), vi) peak activation coordinates were reported in a defined stereotaxic space (Talairach or Montreal Neurological Institute MNI space), vii) article was originally published in English peer-reviewed journal.

Study selection

Demographic, clinical and technical details were extracted from each selected article, including the first author's name, year of publication, type of disease, simple size of patient groups, age, gender, disease duration, treatment, global cognitive status, assessment of apathy and depression (reported in Table 1) and neuroimaging method, type of task, performed analysis and used template (reported in Table 2). Notably, if two or more studies presented different data acquired from the same sample, both were included as separate experiments, if a study found no significant difference between apathetic and control groups, this were entered into the meta-analysis with no coordinates.

ALE meta-analysis

The ALE technique is a meta-analytic approach used to test for above-change convergence of foci reported in individual experiments (Laird et al. 2005; Turkeltaub et al. 2002). The revised version of the ALE algorithm (Eickhoff et al. 2009, 2012) treats foci as 3-dimensional Gaussian probability distributions centered at the given coordinates. The width of the probability distribution depends on empirical estimates of between-subject or between-template variance associated with each single focus, thus resulting in a random-effects analysis. The between-subject variance is weighted by the sample size reported in each experiment included, with larger sample size modeled by smaller Gaussian distributions and providing more reliable approximations of the "true" activation effect. Further, a "modelled activation" (MA) map was computed by merging the probability distributions of all foci within a given experiment. Then, the union of all MA maps in a voxel-wise manner was calculated to determine the voxel-wise ALE scores, that quantified convergence of results across different experiments.

To assess whether the convergence of foci was true or merely the result of random noise, the ALE scores were tested against a null distribution that assumes random spatial

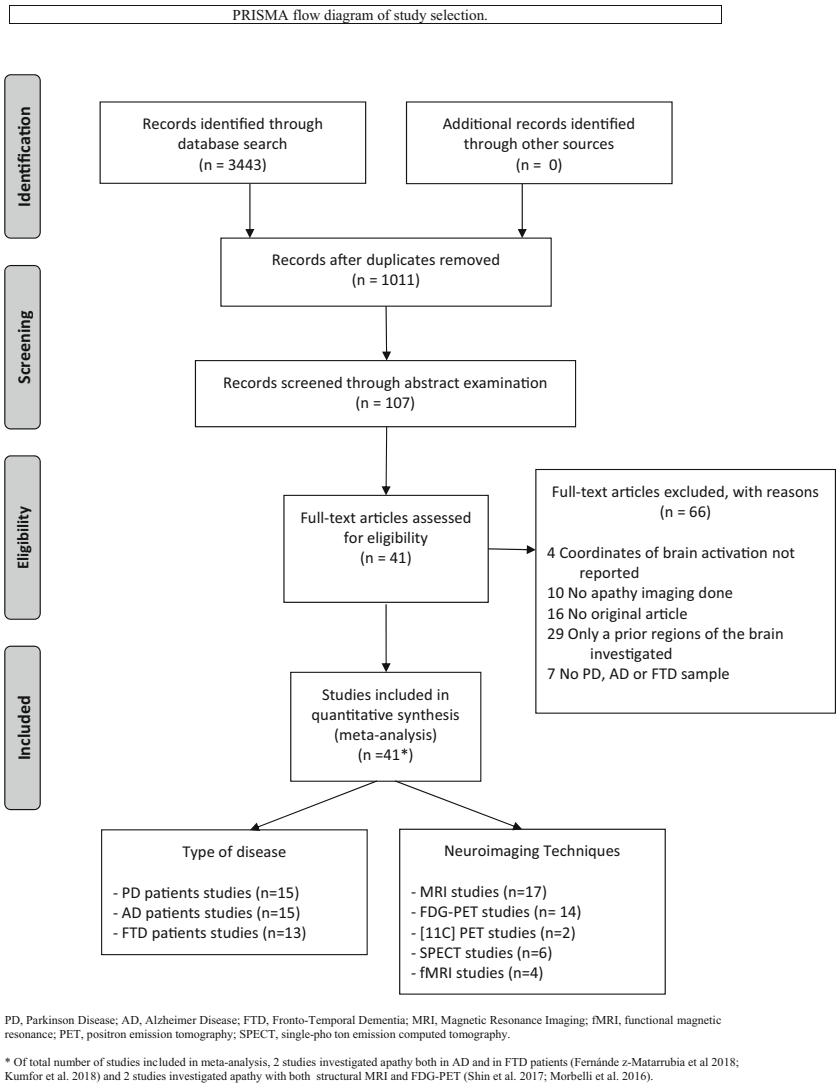

Fig. 1 PRISMA flow diagram of study selection

association between experiments (Eickhoff et al. 2012). Finally, according to a recent simulation study (Eickhoff et al. 2017), the resulting *P*-values were thresholded at $p = 0.05$, cluster-level family-wise error (cFWE) with cluster-forming threshold at voxel-level $p < 0.001$) and transformed into Z-scores for display. To perform ALE meta-analysis we used a specialised software (GingerALE v.2.3.6.) to combine the activation coordinates from several studies (Eickhoff et al. 2009, 2017; Turkeltaub et al. 2002). In the latest version of GingerALE a bug that previously created liberal statistical thresholding has been fixed (Eickhoff et al. 2017). The coordinates reported in Talairach space were converted into MNI space using GingerAle and the ALE results were registered onto MNI brain template using Mango (ric.uthscsa.edu/mango).

In a first step, we compared neuroimaging findings (looking at gray matter volume alteration, metabolic changes, altered brain perfusion and altered functional connectivity, separately) in patients with or without apathy indepedently from clinical diagnosis. According to current recommendations (Eickhoff et al. 2017; Müller et al. 2018) a sample size of at least 17–20 experiments would allow achieving sufficient statistical power in analysis; however, a number of 10–15 experiments would allow performing a "meaningful ALE analysis", even if the risk that observed results can be driven by single experiment is higher (Eickhoff and Bzdok 2013). When the number of primary studies was lower, we decided to conduce a label-based review (Radua and Mataix-Cols 2012) requiring a minimum of 5 studies (Lamsma et al. 2017). Label-based review consisted of calculating the percentages of negative, positive and non-significant results reported for each brain region (Radua and Mataix-Cols 2012). Statistical significance for each primary study was determined by thresholding criteria applied by authors of the study. The null hypothesis was rejected if more than 50% of the results were negative, positive or non-significant (Lamsma et al. 2017). On the basis of brain regions involved in apathy (see Le Heron et al. 2017), we used a parcellation scheme to categorize

Table 1 Summary of 41 studies included in the meta-analysis identifying neural correlates of apathy in PD and dementia

Study	Disease	Number of Subjects	Age (years)	Education (years)	Disease duration (years)	Exclusion criteria
Alzahrani et al. 2016	PD	25	68.7±8.4 (49-80)	10.9±4.5 (5-18)	10.3±5.9	- severe disease stage (H&Y>3) -hystory of psychiatric disorder
Auffret et al. 2017	PD	12 (7M;5F)	65.9±7.2	NR	13.8±3.6	-controindications for apomorphine; -controindications for fludeoxyglucose
Baggio et al. 2015°	PD	25 (20M;5F)	65.6±12.8	8.8±3.5	7.2±4.1	- dementia according to Movement Disorder Society criteria, MMSE - severe disease stage (H&Y>3) - diagnosis of other neurological or psychiatric disease. - pathological magnetic resonance imaging (MRI) findings other than mild white matter (WM) hyperintensities.
Huang et al. 2013	PD	26 (16M;10F)	66.5±1.4	17.8±0.6	5.5±0.7	- diagnosis of other neurological or psychiatric disease - presence of a mass lesion on MRI - prior neurosurgery for PD treatment
Le Jeune et al. 2009	PD	12 (8M;4F)	57.4±8.0	NR	11.2±2.4	- brain atrophy on the basis of a preoperative MRI scan
Reijnders et al. 2010	PD	55 (40M;15F)	62.0±10.1 (42-80)	4.0±1.9	6.6±4.3	- diagnosis of other neurological or psychiatric disease - MMSE < 24 - psychopharmacological treatment
Remy et al. 2005	PD	20 (14M;6F)	58.5±7.9	N.R.	2.8±1.3	- diagnosis of major depression - MMSE<24
Robert et al. 2012	PD	45	60.5±7.8 (47-77)	N.R.	11.3±4.1 (2-24)	- MADRS<21 - MDRS>130
Robert et al. 2014a	PD	36	58.6±7.3 (45-74)	N.R.	11.6±4.03 (6-21)	- major depression - dementia - hystory of stroke - significant cognitive impairment - abnormal structural MRI
Robert et al. 2014b	PD	44 (24M;20F)	56.3±7.5 (36-68)	N.R.	11.4±4.1 (5-21)	- MADRS<21 - MDRS>130
Shen et al. 2018	PD	20	63.3±8.5	11.2±3.1	5.1±4.6	- diagnosis of other neurological or psychiatric disease - contraindications for MRI -intake of psychoactive medications -MMSE≤24 -HDRS-17≥14
Shin et al. 2017	PD	74 (34M;40F)	69.4±8.0	6.1±4.1	5.8±3.6	-fluctuating apathy -history of depression
Skidmore et al. 2013	PD	15 (12M;3F)	62±9	N.R.	N.R.	- MMS<24 - excessive head motion
Terada et al. 2018	PD	40 (16M;24F)	64.7±8.0	N.R.	7.4±4.8	- MMS<24 -RBMT score outside the normal range

Table 1 (continued)

						-SDS>60 -H&Y≠3 - diagnosis of other neurological disease
Thobois et al. 2010	PD	12 (6M;6F)	55.8±4.9	N.R.	10.3±2.2	- an age over 70 years - dementia
Agüera-Ortiz et al. 2017	AD	37 (8M;29F)	82.7±5.8	None:21.6% Primary:73% Superior:5.4%	7.0±2.9	- Levy Body Dementia or other non-AD dementias - severe dementia (Functional Assessment Staging≥7)
Apostolova et al. 2007	AD	17 (7M;10F)	73.9±2.2	13.8±0.5	N.R.	- significant cerebrovascular disease - past medical history of head trauma, seizures, alcohol or substance abuse, psychosis, anxiety, depression or bipolar disorder
Ballarini et al. 2016	AD	27 (15M;12F)	57.70 ± 5.01	15.67 ±3.83	N.R.	- presence of posterior cortical atrophy; - presence of logopenic variant of the primamry progressive aphasia.
Benoit et al. 2002	AD	15 (3M;12F)	77.6±6.1	N.R.	N.R.	- organic personality disorders corresponding to the dysexecutive syndrome (ICD-10 diagnostic criteria)
Benoit et al. 2015	AD	31	73.7±7.5 (54-86)	N.R.	N.R.	- history of head trauma with loss of consciousness - hystory of psychotic or major depressive disorders
Bruen et al. 2008	AD	31 (19M;12F)	77.1±8.6	11.3±3.1	N.R.	- symptoms of depression - claustrophobia - Hachinski Ischaemia >4 - MMSE < 18 - evidence of other degenerative or secondary dementias - history of psychiatric disorders - antipsychotic or psychoactive medication - cholinesterase inhibitor therapy
Fernández-Matarrubia et al. 2018	AD	42 (12M;30F)	76.3±6.9	8.1±5.1	3.2±1.7	- age below 45 or above 90 years -systemic disease with potential impact on cognition -presence of intracranial lesions of significant white matter disease -history of psychiatric disorder -changes on dementia drugs or other medications that could affect cognition in the last 3 months -severe visual or hearing impairments -CDR > 2
Hayata et al. 2015	AD	33	74.1±6.8	5.6±4.8	N.R.	-history of neurological or psychiatric disorders -history of alcohol or substance abuse -exposition to neurotoxic substances -Hachinski Ischaemia >4
Holthoff et al. 2005	AD	17 (6M;11F)	66.7±10.6	11.8±2.9	32.1±24.8 (months)	- permanent brain lesions - delirium - education < 4 years - history of alcohol or substance abuse - history of head trauma with loss of consciousness - history of psychiatric or

Table 1 (continued)

						neurological disorder preceding the onset of memory deficits - epilepsy - major systemic disease with disturbance of brain function
Kang et al. 2012	AD	9 (3M;6F)	68.2±3.9	7.3±6.2	3.6±0.7	- previous or a current neurologic disorder - alcohol or substance abuse; - major systemic disease with disturbance in brain function
Marshall et al. 2007°	AD	14 (13M;1F)	78.6±7.1	12.2±2.5	N.R.	N.R.
Migneco et al. 2001	AD	21 (7M;14F)	77.4±6.3	N.R.	N.R.	N.R.
Ota et al. 2012	AD	21 (8M;13F)	73.8±8.3 (51-86)	N.R.	N.R.	N.R.
Robert et al. 2006°	AD	31 (11M;20F)	73.7±7.5	N.R.	N.R.	- frontotemporal lobar degeneration or Lewy body dementia - history of head trauma with loss of consciousness, psychotic or major depressive disorders
Kumfor et al. 2018	AD/FTD	AD: 53 (28;25F) FTD: 69 (35M;34F)	AD:62.1±6.4 FTD:62.9 ±7.9	AD:12±3 FTD:11.8±2.9	AD: 44.3±28.5 (months) FTD: 48.5±28.5 (months)	-hystory of significant neurological or psychiatric disorder -limited profiency in English
Bertoux et al. 2012	FTD	20 (10M;10F)	68.5±9.1	9.5±4.7	2.7±1.4	- language complaint - systemic illnesses that interfere with cognitive functioning; - vascular lesions seen on MRI - neurological history of vascular dementia - motorneuron disease - major depression - use of anxiolytics or antipsychotics drugs
Borroni et al. 2012	FTD	102 (53M;49F)	65.1±7.3	7.3±3.3	N.R.	- neurological and psychiatric disorders - a past history of alcohol abuse, psychosis, or major depression
Eslinger et al. 2012	FTD	12	65.3±12.6	14.8±4.7	N.R.	- motor disorder - medications that interfere with attentiveness
Farb et al. 2013	FTD	16 bvFTD: 8 (4M;4F) SD: 8 (4M;4F)	66.7±2.5 64.5±3.3	16.0±0.8 17.1±0.9	N.R.	- history of any neurological or psychiatric disorders -CDR≥3
Fernandèz-Matarrubia et al. 2018	FTD	42 (25M;17W)	71.6±8.3	8±4.9	3.8±2.1	-age below 45 or above 90 years -systemic disease with potential impact on cognition -presence of intracranial lesions of significant white matter disease

Table 1 (continued)

						-history of psychiatric disorder -changes on dementia drugs or other medications that could affect cognition in the last 3 months -severe visual or hearing impairments -CDR > 2
Franceschi et al. 2005	FTD	12 (6M;6F)	68 (56-80)	8 (2-13)	28 (12-72)	- history of cerebral ischemic event, alcohol abuse, head injury - hystory of major medical illness - hystory of depression
Massimo et al. 2009	FTD	9 (7M;2F)	63.0±10.6	16.9±2.1	43.4±23.4	- diagnosis of other neurological or psychiatric
Morbelli et al. 2016	FTD	13 (5M;8F)	71.6±5.8	12.0±8.9	N.R.	- diagnosis of other neurological or psychiatric
Peters et al. 2006	FTD	13	N.R.	N.R.	N.R.	N.R.
Powers et al. 2014	FTD	11 (7M;4F)	60.5±2.0	N.R.	N.R.	-history of cerebral ischemic event, head injury and hydrocephalus; -history of medical conditions associated with cognitive difficulty -diagnosis of other neurological or psychiatric
Rosen et al. 2005	FTD	23	64.8±9.4	N.R.	N.R.	N.R.
Zamboni et al. 2008	FTD	62 (29M;33F)	61.2±1.0	15.5±0.4	N.R.	N.R.

Study	Treatment (% of patients taking therapy)	UPDRS III	LED	Global Cognitive Status	Apathy	Depression
Alzahrani et al. 2016	N.R.	N.R.	N.R.	MMSE: 27.22±1.8	NPI-A≥1	Excluded
Auffret et al. 2017	N.R.	16.5±6.6	832.5±377.6	N.R.	LARS: -24.2±7.0 LARS-i: -24.2±7.3	MADRS 6.3 ±4.3
Baggio et al. 2015°	Antidepressant: 20% Antiparkinsonian medication	15.5±7.9	845.2± 471.3	MMSE: 28.9±1.1	AS: 19.3±4.1	Not excluded BDI-II: 14.8±5.3
Huang et al. 2013	Antiparkinsonian medication	N.R.	N.R.	MMSE: 29.2±0.2	AES: 31 (18-48)*	Not-excluded BDI-II: 8 (1-21)*
Le Jeune et al. 2009	Antiparkinsonian medication	5.5±3.4	N.R.	MDRS: 140±3.2	AES: 39.1±6.5	Not-excluded MADRS: 6.2±8.2
Reijnders et al. 2010	Dopamine agonist: 62%	17.3±4.9	N.R.	MMSE: 27.8±1.9	LARS: -22.2±6.8 AES: 28.7±6.0 NPI-A: 2.1±2.3	Not Excluded HDRS=6.2 ± 3.4
Remy et al. 2005	Antidepressant: 32%	23.1±9.0	477.5±257.8	N.R.	AES: 5.2±2.7	Not excluded BDI: 5.5±2.5
Robert et al. 2012	Antiparkinsonian medication	on state: 8.4±5.9 off state: 29.9±12.2	1215±492.7	MDRS: 139.3±0.5	AES: 35.1±6.6	Excluded MADRS: 5.7±0.7
Robert et al. 2014a	Antiparkinsonian medication Antidepressant: 22%	7.9±5.4	1276.8±507.5	MDRS: 139.7±3.1	AES: 58.6±7.3	Excluded MADRS: 5.7±4.7
Robert et al. 2014b	Antiparkinsonian medication	on state: 7.5+5.2	1280.8±632.4	MDRS: 140.6±2.5	AES: 31.6±7.1	Excluded

Table 1 (continued)

		off state: 32.6+12.8				MADRS: 4.45±4
Shen et al. 2018	Antiparkinsonian medication	21.8±8.9	423.7±261.6	MMSE: 28.5±1.3	AS: 19.4±4.4	Excluded HDRS-17: 4.20±3.21
Shin et al. 2017	N.R.	23.8±14.2	692.7±393.9	MMSE: 25.3±3.8	AS: 204±5.0	Excluded
Skidmore et al. 2013		37±13	1079± 639	MMSE: 27± 3 MoCA: 25±3	LARS-self: -21±5 LARS-hetero: -18±12	Not Excluded HRSD: 13±6
Terada et al. 2018	N.R.	27.2±8.2	N.R.	MMSE: 27.1±2.0	FrSBE	Excluded SDS: 40.7±9.4
Thobois et al. 2010	Antiparkinsonian medication	36.0±16.3	N.R.	N.R.	SAS: 11.3±7.9	Not Excluded BDI: 17.9±10.2
Agüera-Ortiz et al. 2017	N.R.	-	-	sMMSE: 15.3±9.0	APADEM-NH: 31.1±18.5 NPI-A: 6.2±3.4	Not Excluded NPI-D: 1.5±2.9
Apostolova et al. 2007	Antidepressant: 17% Antipsychotics: 0% Cholinesterase inhibitors: 76%	-	-	MMSE: 20.5±1.5	NPI-A: 5.73 ± 0.9	Excluded NPI-D
Ballarini et al. 2016	N.R.	-	-	MMSE: 20.78±6.33	NPI-A: 3.74±4.04	Not Excluded NPI-D: 1.56±2.89
Benoit et al. 2002	Antidepressant: 20%	-	-	MMSE: 19.8±3.7	NPI-A: 6.9±2.7	Excluded NPI-D: 2.4±2.8
Benoit et al. 2015	Antidepressant: 20%	-	-	MMSE: 22.8±9.3	AI: 10.7±11	Excluded NPI-D: 2.6±3.4
Bruen et al. 2008	N.R.	-	-	MMSE: 23.3±2.8	NPI-A: 3.2±3.0	Excluded NPI-D: 0.7±1.6
Fernández-Matarrubia et al. 2018	N.R.	-	-	MMSE: 21.24±5.33	LARS: -4.52±17.99 FBI-A: 1.56±1.42 NPI-A: 5.29±5.27	Excluded HDRS-17: 3.55±4.29
Hayata et al. 2015	N.R.	-	-	MMSE: 16.6±5.7	NPI-A: 3.72±2.91	Not excluded NPI-D: 3.69±0.64
Holthoff et al. 2005	Cholinesterase inhibitors: 5% Piracetam:11.7%	-	-	MMSE: 22.1±4.1	NPI-A≥4	Excluded HAM-D: 4.1±2.0
Kang et al. 2012	N.R.	-	-	MMSE: 17.2±4.9	NPI-A: 5.9±2	Excluded MADRS: 12.9±5.2 NPI-D: 0.9±0.9
Marshall et al. 2007°	No cholinergic medication or memantine	-	-	MMSE: 16.8±5.0	SANS-AD apathy: 2.7±0.9 SANS-AD emotional withdrawal: 1.9±0.9	Not excluded NRS-D: 0.7±0.9
Migneco et al. 2001	psychiatric medication: 4% Antidepressant: 19%	-	-	MMSE: 20±3.8	NPI-A: 7.2±2.7	Excluded NPI-D: 2.3±1.7
Ota et al. 2012	no antidepressants donezepil: 5%	-	-	MMSE: 19.2±2.6	AS: 21.0±7.8	Not excluded
Robert et al. 2006°	no cholinergic medication Antidepressant: 9%	-	-	MMSE: 22.8±3	AI: 10.7±11	Excluded NPI-D: 2.6±3.5
Kumfor et al. 2018	N.R.	-	-	ACE: AD: 66.9±16.2	NPI-A AD-A: 60%	Not excluded

Table 1 (continued)

				FTD: 71.8±117.4	FTD-A: 84%	
Bertoux et al. 2012	N.R.	-	-	MMSE: 24.4±4.2	SEA-A: 7.1±2.8 AS: 23.1 ± 6.2	Excluded
Borroni et al. 2012	N.R.	-	-	MMSE: 22.1±5.3	FBI-A	Excluded
Eslinger et al. 2012	N.R.	-	-	MMSE: 23.3±5.4	AES-S: 34.36 AES-I: 58.25	Not Exluded BDI: 14.67±7.39
Farb et al. 2013	N.R.	-	-	N.R.	FBI-A: 20.4 ± 2.7 FBI-A: 13.9 ± 2.3	Not excluded
Fernandèz-Matarrubia et al. 2018	N.R.	-	-	MMSE: 22.86±5.89	LARS: 8.29±15 FBI-A: 2.42±1.12 NPI-A: 9.43±4.42	Excluded HDRS-17: 3.91±3.05
Franceschi et al. 2005	N.R.	-	-	MMSE: 23.8	NPI-A: 5 Clinical diagnosis of apathy	Not Excluded HDRS: 10
Massimo et al. 2009	N.R.	-	-	N.R.	NPI-A	Excluded NPI-D
Morbelli et al. 2016	N.R.	-	-	MMSE: 26.6±1.5	NPI-A: 3.8±2.8	Not excluded NPI-D: 4.3±4.1
Peters et al. 2006	N.R.	-	-	N.R.	NPI-A: 9.8	Not excluded
Powers et al. 2014	N.R.	-	-	MMSE: 25.0±1.4	NPI-A: 5.2±1.3	Not excluded NPI-D: 1.6±0.8
Rosen et al. 2005	N.R.	-	-	MMSE: 21±7.7	NPI-A	Not exluded NPI-D
Zamboni et al. 2008	N.R.	-	-	N.R.	FrSBE: 95.6±3.3	Not Excluded

° controlling for the presence of depression

M, Males; F, Females; PD, Parkinson Disease; AD, Alzheimer Disease; FTD, Fronto-Temporal Dementia; AS, Apathy Scale; AES, Apathy Evaluation Scale, LARS, Lille Apathy Rating Scale; APADEM-NH, Apathy in Dementia – Nursing; NPI, Neuropsychiatric Inventory, NPI-A, Neuropsychiatric Inventory-apathy subscale, UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn e Yahr; LED, levodopa equivalent dose; MMSE, Mini Mental State Examination; sMMSE, severe Mini Mental State Examination; MDRS, Mattis Dementia Rating Scale; MoCA, Montreal Cognitive Assessment; RBMT, Rivermead Behavioral Memory Test; ACE, Addenbrooke's Cognitive Examination; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Scale; FrSBE, Frontal Systems Behavior Scale; FBI, Frontal Behavioral Inventory; BDI, Beck Depression Inventory; SDS, Self-Rating Depression Sclae; SANS-AD; Scale on the Assessment of Negative Symptoms in AD; SEA-A, Social Cognition and Emotional Assessment; CDR, Clinical Dementia Rating; N.R., Not Reported. * median

results. In particular, frontal regions, that are either directly or indirectly connected to the striatum and implicated in normal motivated behavior (Le Heron et al. 2017), have been subdivided on the basis of the human Brainnetome Atlas (see Fan et al. 2016) in: superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, orbital gyrus, insular lobe and cingulate gyrus. The remaining cerebral cortex was divided into temporal, parietal, and occipital cortex (see Brainnetome Atlas; Fan et al. 2016).

Result

As of July 2018, a total of 3443 articles were retrieved across the three databases. We did not find additional articles from manuscript reference lists. After filtering for duplicates, there were a total of 1011 articles for screening by title and abstract (Fig. 1) and 107 full-text articles were reviewed for eligibility according to the previously described inclusion criteria. Of these 107 studies, 5 did not report activation coordinates (Ballarini et al. 2016; Gesquière-Dando et al. 2015; Hahn et al. 2013; Stanton et al. 2013; Starkstein et al. 2009), but we obtained data from the Ballarini et al. (2016) contacted via e-mail. Moreover, 7 studies did not investigate neural correlates of apathy specifically in AD, PD and/or FTD patients sample (Delrieu et al. 2015; Hollocks et al. 2015; Jonsson et al. 2010; Lavretsky et al. 2008; Lohner et al. 2017; Schroeter et al. 2011; Stanton et al. 2013). After careful scrutiny (see Fig. 1 for details), 41 publications were considered appropriate and used in the meta-analysis. Notably, none of these presented different data acquired from the same sample, 2 studies investigated apathy with both structural MRI and functional neuroimaging (Shin et al. 2017; Morbelli et al. 2016), 2 investigated apathy both in AD and in FTD patients (Fernández-Matarrubia et al. 2018; Kumfor et al. 2018).

Studies included in meta-analysis compared patients with or without apathy (AD-A versus AD-NA patients, 6 studies; PD-A versus PD-NA, 6 studies; FTD-A versus FTD-NA, 2 studies), or patients with apathy and healthy controls (AD-A versus HC, one study; PD-A versus HC, 5 studies; FTD-A versus HC, 3 studies); correlations between neuroimaging with scores on apathy scales were reported in 32 primary studies. One study found no difference between AD-A and AD-NA groups and was thus entered into the meta-analysis with no coordinates (Hayata et al. 2015).

ALE meta-analysis: Structural and metabolic alterations associated with apathy

Seventeen studies focused on gray matter volume alterations associated with apathy. Sixteenstudies reported decreased volumes, whereas only 1 reported both decreased and increased volumes; therefore we did not conduct a separate meta-analysis for gray matter volume increases associated with apathy. These 17 studies included data from 605 patients (194 PD, 192 AD, 219 FTD) and reported 176 foci of gray matter volume decreases associated with apathy (see Table 2). Our meta-analysis of structural MRI studies revealed two cluster of significant convergence between the studies (see Table 3, Fig. 2) in the left inferior frontal gyrus (BA 46) and left basal ganglia (caudate nucleus and putamen).

Our research analysis of other neuroimaging techniques revealed that 14 studies reported metabolic changes associated with apathy using 18F-fluorodeoxyglucose PET, 2 studies using 11C-raclopride-PET to investigate apathy in PD; 6 studies analyzed brain perfusion associated with apathy using SPECT and 4 studies analyzed funcional connectivity using fMRI (see Table 2). Therefore, we performed ALE meta-analysis on FDG-PET studies ($n = 14$) only, and interpreted the results cautiously. The fourteen FDG-PET studies that showed metabolic activations in patients with apathy (see Table 2) included data from 429 patients (249 PD, 100 AD, 80 FTD) and reported 95 foci of hypometabolism. Our meta-analysis would reveal only one cluster of significant convergence between the studies in the left inferior frontal gyrus (BA 45; see Table 3, Fig. 2).

Disease-specific alterations associated with apathy

Our review of structural MRI studies revealed that 4 studies investigated neural correlates of apathy in PD, 5 in AD and 7 in FTD (see Table 2). As regards other neuroimaging techniques studies, 7 studies reported metabolic changes (FDG-PET) associated with apathy in PD, 4 in AD and 4 in FTD (see Table 2); 3 studies reported altered functional connectivity (fMRI) associated with apathy in PD and 1 in FTD; 5 studies reported altered brain perfusion (SPECT) associated with apathy in AD and 1 in FTD. We performed label-based review when a minimum of 5 studies were found (Lamsma et al. 2017).

Label-based review of MRI studies in AD (5 studies, 139 patients) showed that anterior cingulate cortex (in particular BA 24; 60%, 3 out of 5), without a clear cerebral lateralization, was the only region for which more than half of the results were negative, indicating that apathy in AD was significantly associated with reduced gray matter volume in this area (see Fig. 3). Label-based review of MRI studies in FTD (7 studies, 150 patients) did not show significant finding for all regions but inferior frontal gyrus (in particular, BA 44, 45; 70%, 5 out of 7) and parietal cortex (in particular right BA 40; 60%, 4 out of 7), for which more than half of the results were negative; therefore, apathy in FTD would be associated with reduced gray matter volume in these areas (see Fig. 3).

Label-based review of FDG-PET studies in PD (7 studies, 249 patients) did not reveal significant findings (see Fig. 3).

Table 2 Neuroimaging characteristics of 41 studies included in the meta-analysis

Study	Disease	Neuroimaging Tecnique	Task	Analysis	Template	Foci
MRI						
Alzaharni et al. (2016)	PD	1.5 MRI	Resting State	Comparison among groups (PD-A < PD-NA, PD-A < HC)	Talairach	27
Reijnders et al. (2010)	PD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	28
Terada et al. (2018)	PD	MRI	Resting State	Correlation between apathy score and gray matter density	Talairach	1
Agüera-Ortiz et al. (2017)	AD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	13
Apostolova et al. (2007)	AD	MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	3
Bruen et al. (2008)	AD	1.5 T MRI	Resting State	Correlation between apathy scores and gray matter density	Talairach	11
Hayata et al. (2015)	AD	3 T MRI	Resting State	Correlation between apathy scores and cortical thickness	Talairach	0
Ota et al. (2012)	AD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	4
Kumfor et al. (2018)	AD/FTD	MRI	Resting State	Correlation between apathy score and gray matter density	MNI	22
Bertoux et al. (2012)	FTD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	1
Eslinger et al. (2012)	FTD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	4
Massimo et al. (2009)	FTD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	35
Powers et al. (2014)	FTD	3 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	2
Rosen et al. (2005)	FTD	1.5 T MRI	Resting State	Correlation between apathy scores and gray matter density	MNI	1
Zamboni et al. (2008)	FTD	1.5 T MRI	Resting State	Correlation between apathy scores and gray matter density	Talairach	12
FDG-PET						
Auffret et al. (2017)	PD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	Talairach	18
Huang et al. (2013)	PD	[18F]FDG-PET	Resting State	Comparison among groups (PD-A < HC, PD-A > HC) Correlation between apathy scores and glucose metabolism	MNI	15
Le Jeune et al. (2009)	PD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	Talairach	8
Robert et al. (2012)	PD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	MNI	6
Robert et al. (2014)a	PD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	Talairach	1
Robert et al. (2014)b	PD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	Talairach	1
Ballarini et al. (2016)	AD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	MNI	8
Fernández-Matarrubia et al. (2018)	AD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	MNI	2
Holthoff et al. (2005)	AD	[18F]FDG-PET	Resting State	Comparison among groups (AD-A < AD-NA)	Talairach	2
Marshall et al. (2007)	AD	[18F]FDG-PET	Resting State	Comparison among groups (AD-A < AD-NA)	Talairach	4
Fernández-Matarrubia et al. (2018)	FTD	[18F]FDG-PET	Resting State	Correlation between apathy scores and glucose metabolism	MNI	11
Franceschi et al. (2005)	FTD	[18F]FDG-PET	Resting State	Comparison among groups (FTD-A < FTD-NA; FTD-A < HC; FTD-A > FTD-NA)	MNI	23

Table 2 (continued)

Study	Disease	Neuroimaging Tecnique	Task	Analysis	Template	Foci
Peters et al. (2006)	FTD	[18F]FDG-PET	Resting State	Comparison among groups (FTD-A < FTA-NA)	MNI	2
MRI & FDG-PET						
Shin et al. (2017)	PD	3 T MRI [18F]FDG-PET	Resting State	Comparison among groups (PD-A < PD-NA; PD-A < HC; PD-A > PD-NA; PD-A > HC) Correlation between apathy scores and glucose metabolism Correlation between apathy scores and gray matter density	Talairach	21
Morbelli et al. (2016)	FTD	1.5 T MRI FDG-PET	Resting State	Comparison among groups (FTD-A < HC)	Talairach	9
[11C] PET						
Remy et al. (2005)	PD	[11C]RTI-32 PET	Resting State	Correlation between apathy scores and glucose metabolism	Talairach	2
Thobois et al. (2010)	PD	[11C]-raclopride PET	Resting State	Comparison among groups (PD-A > PD-NA)	MNI	11
fMRI						
Baggio et al. (2015)	PD	3 T fMRI	Resting State	Comparison among groups (PD-A < PD-NA, PD-A < HC) Correlation between apathy scores and functional connectivity	MNI	31
Shen et al. (2018)	PD	fMRI	Resting State	Comparison among groups (PD-A < PD-NA; PD-A < HC) Correlation between apathy score and low frequency fluctations	MNI	5
Skidmore et al. (2013)	PD	3 T fMRI	Resting State	Correlation between apathy scores and amplitude of low frequency fluctuations	MNI	8
Farb et al. (2013)	FTD	3 T fMRI	Resting State	Comparison amoung groups (FTD-A < HC) Correlation between apathy scores and gray matter density	MNI	1
SPECT						
Benoit et al. (2002)	AD	99 m Tc-ECD SPECT	Resting State	Comparison among groups (AD-A < AD-NA, AD-A < HC)	Talairach	11
Benoit et al. (2015)	AD	99 m Tc-ECD SPECT	Resting State	Correlation between apathy scores and brain perfusion	Talairach	6
Kang et al. (2012)	AD	99 m Tc-HMPAO SPECT	Resting State	Comparison among groups (AD-A < AD-NA)	MNI	15
Migneco et al. (2001)	AD	99 m Tc-ECD SPECT	Resting State	Comparison among groups (AD-A < AD-NA)	Talairach	1
Robert et al. (2006)	AD	ECD-SPECT	Resting State	Comparison among groups (AD-A < AD-NA) Correlation between apathy scores and glucose metabolism	Talairach	5
Borroni et al. (2012)	FTD	ECD-SPECT	Resting State	Correlation between apathy scores and brain perfusion	Talairach	3

PD, Parkinson Disease; *AD*, Alzheimer Disease; *FTD*, Fronto-Temporal Dementia; *−A*, with apathy; *-NA*, without apathy; *HC*, healthy subjects; *MNI*, Monteral Neurological Institute; *MRI*, Magnetic Resonance Imaging; *fMRI*, functional magnetic resonance; *[18F]FDG-PET*, [18F]fluoro-D-glucose positron emission tomography; *99mTc-HMPAO SPECT*, (Technetium-99 m)-hexamethyl-propylene-aminoxime single-photon emission computed tomography; *ECD*, ethyl cysteinate dimer

Label-based review of SPECT studies in AD showed a significant decreased perfusion in anterior cingulate cortex (in particular in BA 24 and BA 32; 80%, 4 out of 5) and in superior frontal gyrus (in particular, medial BA 10, 80%, 4 out of 5), whithout a clear cerebral lateralization.

For more details see Fig. 4 in Supplementary Material.

Discussion

To our knowledge, the current study provides the first quantitative analysis of hypometabolism and gray matter volume reductions in neurological patients (PD, AD, FTD) with apathy. Overall meta-analysis provided significant independent evidence of altered brain structure and hypometabolism within the left inferior frontal gyrus (BA 45, 46) associated to apathy. The inferior frontal gyrus is tightly connected with the dorsal portion of the caudate nuclei (in particular the head, Selemon and Goldman-Rakic 1985; Arikuni and Kubota 1986; Levy and Dubois 2006) within a frontal-subcortical circuit mostly contributing to executive functions and it is part of a network, including supplementary motor cortex, anterior cingulate cortex and the thalamus, contributing to willed actions (Jahanshahi and Frith, 1998; Habas et al. 2009; Wu et al. 2016). In particular, this area would be involved in rule-finding, set-shifting, maintenance of goals and subgoals, all

Table 3 Meta-analysis results of structural and metabolic alterations associated with apathy in neurodegenerative disorders

Region	BA	H	Volume	MNI Coordinates
Structural Meta-Analysis (Decreased gray matter volume associated with apathy)				
Inferior Frontal Gyrus	46	L	560	−46 24 24
				−48 24 18
Basal Ganglia (caudate nucleus, lentiform nucleus of putamen)		L	536	−10 16–4
				−14 14–8
FDG-PET Meta-Analysis (Hypometabolism associated with apathy)				
Inferior Frontal Gyrus	45	L	1416	−54 30 2

H, Hemisphere; *R*, Right; *L*, Left; *BA*, Brodmann areas; *MNI*, Montreal Neurological Institute; *FDG-PET*, Fluorodeoxyglucose positron emission tomography

processes that underlie action planning and regulation (Tekin and Cummings 2002; Levy and Dubois 2006).

Thus, metabolic changes in BA 45 would be mainly associated with difficulties in maintenance, selection and retrieval mental representation of goal and subgoals, whereas structural changes of BA 46 wold be mainly involved with difficulties in manipulation and monitoring mental representation of them (Blumenfeld et al. 2013).

These impairments would lead to hampered elaboration of goal-directed behaviors, reducing them both quantitatively and qualitatively (Levy and Dubois 2006). 'Cognitive inertia' is indeed frequently observed in patients with neurodegenerative disorder and is associated with difficulties in executive tasks requiring activation of mental strategies to generate rules and to retrieve words or information from declarative memory (i.e. Wisconsin Card Sorting Test, Trail Making Test; McPherson et al. 2002; Meyer et al. 2014; Santangelo et al. 2015; Raimo et al. 2016).

While the results of our meta-analysis on all studies showed grey matter loss and hypometabolism in the left inferior frontal gyrus, our label-review suggested the existence of disease-specific patterns of brain atrophy and hypoperfusion in AD and FTD.

In AD patients apathy woud be associated with atrophy and hypoperfusion in the anterior cingulate cortex (BA 24); hypometabolism would also be present in additional prefrontal medial regions (BA 32) and in superior frontal gyrus (BA 10), without a clear cerebral lateralization. The anterior cingulate cortex has subcortical connections with limbic striatum and reciprocal cortical connections with the orbitofrontal cortex and the motor areas (Bonelli and Cummings 2007). According to the neuroanatomical models of Tekin and Cummings (2002) and of Levy and Dubois (2006), the dorsal part of the anterior cingulate cortex (BA 24 and 25) would have a fundamental role in motivation and reward systems and it would be mainly involved in auto-activation, i.e. in activating thoughts or initiating motor programs necessary to complete behaviors. Several studies showed a hypoactivation within the anterior cingulate cortex during tasks of emotion processing (Sterzer et al. 2005; Stadler et al. 2007) and response inhibition (Zold et al. 2007). The clinical picture related to a dysfunction of the anterior cingulate cortex would be characterized by a failure to reach the threshold of initiation/activation of thoughts or actions on an internal basis, but not in response to external stimuli (behavioural apathy; Marin 1991; Levy and Dubois 2006).

The medial frontal gyrus (BA 10) would play a fundamental role in genesis of apathy due to its functional and structural connectivity (Ray et al. 2015; Moayedi et al. 2015). The left lateral part of BA 10 is functionally connected to nodes of the executive control network, including the supplementary motor area, the ventrolateral premotor cortex, the lateral parietal cortex, the dorsolateral prefrontal cortex and the anterior insula bilaterally and has high co-activations with the anterior cingulate, the middle frontal gyrus extending into the inferior frontal gyrus, insula bilaterally and the left fusiform gyrus and the right caudate (Tekin and Cummings 2002; Ray et al. 2015; Moayedi et al. 2015). In addition, the left middle part of BA 10 is functionally connected to nodes of the default-mode network and has high level of co-activations with the left superior and inferior frontal gyrus, the left caudate and lentiform nucleus, the left superior temporal gyrus and the amygdalae bilaterally (Bonelli and Cummings 2007; Ray et al. 2015; Moayedi et al. 2015). This functional architecture allows BA 10 to play a key role in evaluation of internal representations (Christoff and Gabrieli 2000), including evaluation of the potential reward value of future actions (Boorman et al. 2009) and to select and activate the appropriate behaviour based on feedback from external environment. Thus, dysfunction of BA 10 would be implicated in alteration of motivational processing for its connections with medial orbital frontal cortex, that has a central role in associating emotion or affect information with planned or ongoing behaviour (Pochon et al. 2002; Kringelbach 2005; Wallis 2007) and in determining appropriate time, place and strategy for environmentally elicited behavioural responses (O'Doherty et al. 2001; Elliott et al. 2003).

In patients with FTD, our label-based analysis suggested the presence of grey matter loss in the inferior frontal gyrus (BA 44, 45) and in the right inferior parietal gyrus (BA 40). As

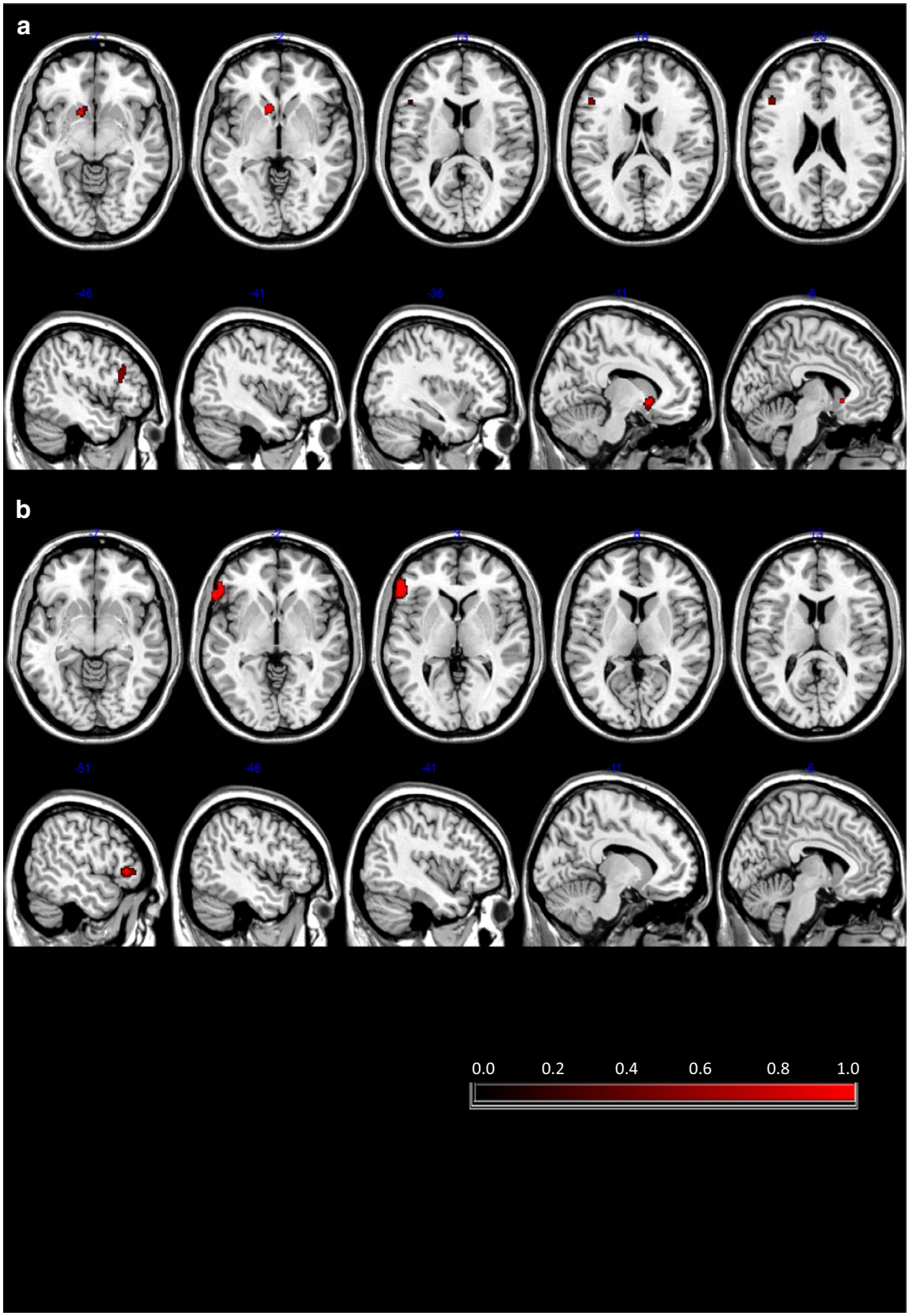

Fig. 2 **a** Activation map for decreased gray matter volume associated with apathy in neurodegenerative disorders (176 foci, 605 patients). **b** Activation map for brain hypometabolism associated with apathy in neurodegenerative disorders (95 foci, 429 patients). Threshold for significance determinated by cluster-level inference ($p = 0.05$, 1000 permutations with cluster forming threshold at voxel level $p < 0.001$)

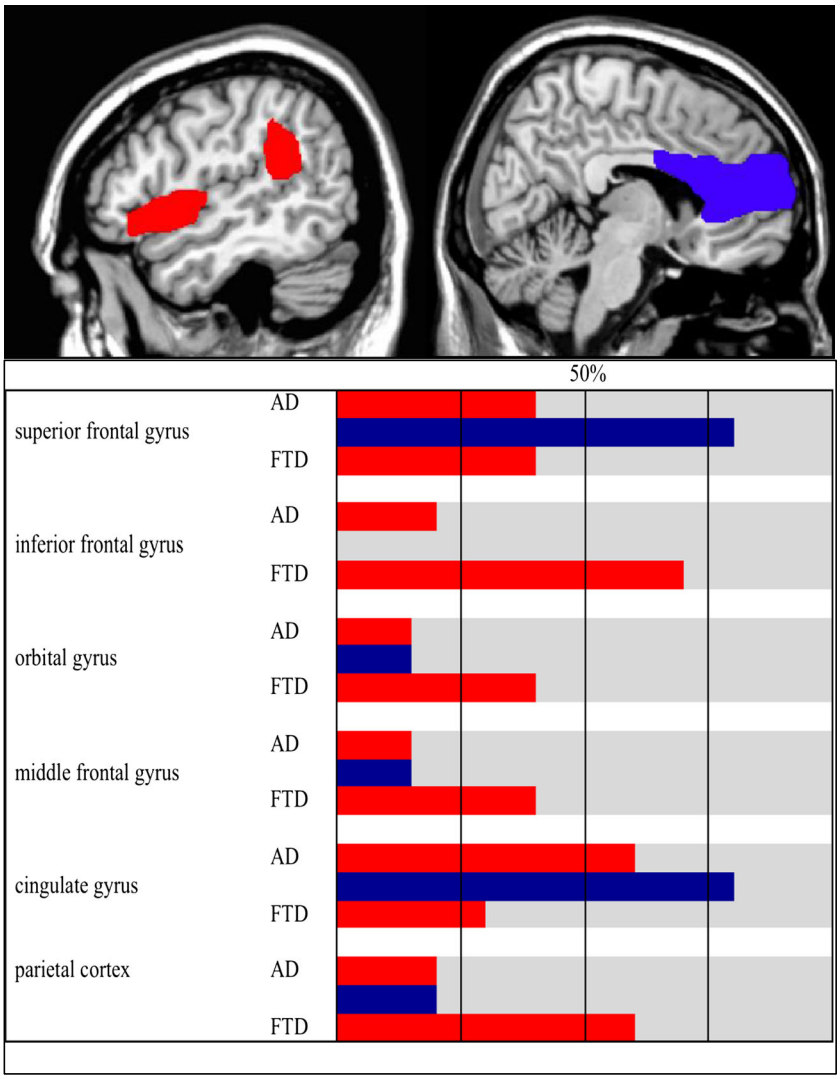

Fig. 3 Percentages of neuroimaging studies indicating grey matter reduction (in red), or hypoperfusion (in blue) in different brain regions associated with apathy in AD and FTD (for more details see Supplemental Fig. 4). AD, Alzheimer's disease; FTD, Frontotemporal dementia

stated above, the inferior frontal gyrus would be associated to the ability to generate and maintain purposeful behaviors (Levy and Dubois 2006), whereas the right inferior parietal cortex would have a key role in intentional movements and movement awareness (Kos et al. 2016, 2017). These regions would constitute a fronto-parieto-striatal network associated to alterations in starting motor programs and in motivation (Kos et al. 2016), thus being a critical component of the auto-activation subdomain of apathy (Levy and Dubois 2006).

Meta-analytic approaches such as the current one have a number of limitations. First of all, these analyses are limited by detail and quality of the original research studies. In the present case, problems might arise from heterogeneity of tools used for assessment of apathy (e.g., specifically validated scales or general scales for neuropsychiatric symptoms; moreover, only some studies assessed distinct subtypes of apathy), from comorbid diagnosis with depression (some studies investigated "pure apathy" whereas others included depressed patients), or from differences in experimental design (some studies compared apathetic patients with healthy controls, others compared data of patients with or without apathy). The relatively low number of available studies led us to analyse together those comparing apathetic patients vs. non-apathetic patients, and those comparing apathetic patients vs. controls and also correlation studies.

Secondly, we aimed at investigating the neural correlates of apathy in the three diagnostic populations where apathy is most frequent and most frequently assessed (AD, FTD, PD), and thus did not consider studies assessing neural correlates of apathy in other neurological disorders and/or in samples including patients with various type of dementia and/or mild cognitive impairment. Finally, meta-analysis studies should ideally include a minimum of 17 studies in each dataset to obtain sufficient statistical power (Eickhoff et al. 2017), therefore, the current analysis on metabolic changes runs the risk of being underpowered, and label-based results should be interpreted with caution.

Conclusion

The present meta-analytic study demonstrated that structural and metabolic changes in patients with apathy are mainly localized within the left inferior frontal gyrus which is part of the central executive network, activated during stimulus-driven cognitive or affective processing. The relatively limited pool of studies and the different neuroimaging techniques did not allow us to perform a quantitative investigation of brain patterns related to apathy in different neurodegenerative disorders. Future studies are necessary to confirm the present results, but knowledge about the neural underpinnings of apathy is crucial for understanding its clinical characteristics in neurodegenerative diseases and for developing appropriate strategies of treatment in clinical practice.

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