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A review of neuroimaging findings of apathy in Alzheimer's Disease

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Abstract

Background—Apathy is one of the most frequent 'behavioral and psychological signs and symptoms of dementia' (BPSD) encountered in Alzheimer's Disease (AD). There is a growing interest in the early diagnosis of apathetic elderly patients in the community since apathy has been associated with reduced daily functioning, caregiver distress, and poor outcome. The generalization of neuroimaging techniques might be able to offer help in this domain.

Methods—Within this context we conducted an extensive electronic search from the databases included in the National Library of Medicine as well as PsychInfo and Google Scholar for neuroimaging findings of apathy in Alzheimer's Disease.

Results—Neuroimaging findings lend support to the notion that frontal-subcortical networks are involved in the occurrence of apathy in AD.

Conclusions—Longitudinal studies comparing patients and normal individuals might allow us to infer on the association between apathy and neurodegenerative diseases and what can brain imaging markers tell us about the characterization of this association, thus revealing disease patterns, helping to distinguish clinically distinct cognitive syndromes, and allowing predictions.

Keywords

neuroimaging studies; apathy; Alzheimer's Disease; dementia; mild cognitive impairment; depression; frontal-subcortical networks; anterior cingulate cortex

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CT designed the review and wrote the paper. AP and SK assisted with the writing of the paper. AP and CL supervised the whole process.

Introduction

Besides the cognitive aspects, clinicians often encounter complex disorders of affect and behaviour in patients with Alzheimer's Disease (AD), also known as BPSD that are responsible for increased rates of hospitalization, increased morbidity, caregiver stress and cost of care. The prevalence of these symptoms varies according to the disease stage, the specific population studies, as well as the study context. Applying the Neuropsychiatric Inventory (NPI) to an American population of patients with AD, Mega *et al.* (1996) found that 88% of subjects with AD had BPSD, of which apathy was the most frequent, reported to occur in 29% to 72% of patients with AD (Cummings, 1997; Benoit *et al.*, 1999; Lyketsos *et al.*, 2000, 2002).

What is apathy?

Apathy has been defined as the absence or lack of feeling, emotion, interest, concern, or motivation not attributable to a decreased level of consciousness, cognitive impairment, or emotional distress (Marin, 1990). Starkstein and colleagues (2001) have proposed diagnostic criteria of apathy which specify the following as the core features of apathy: diminished motivation, diminished initiative and interest, and blunting of emotions. In a recent article, (Robert *et al.*, 2009) by a group of experts with international representation, apathy is defined as a disorder of motivation that persists over time and should meet the following requirements: diminished motivation must be present for at least four weeks; secondly two of the three following items (reduced goal-directed behaviour; reduced goal-directed cognitive activity, and blunting of emotions) should also be present. Last but not least there should be functional impairments which can be identified and be attributed to apathy. For a review of all proposals of diagnostic criteria please see (Robert *et al.*, 2009; Mulin *et al.*, 2011).

Apathy is also encountered in several neuropsychiatric disorders; it is present in up to 90% of patients with fronto-temporal dementia, dementia with Lewy bodies and progressive supranuclear palsy, 40% of those with cortico-basal degeneration, and 20% of those with Parkinson's disease (Cummings *et al.*, 1996; Cummings, 1997); Some degree of apathy is observed in brain injuries and cerebrovascular lesions concerning frontal lobes and is related in large degree to lesion location (Marin, 1990; Cummings *et al.*, 1996).

Apathy in dementia

In AD apathy has been associated with reduced daily functioning, caregiver distress, and poor outcome (Landes *et al.*, 2001). Apathy frequently complicates the course and management of dementia by contributing to functional disability and self-neglect (Landes *et al.*, 2001) and seems to be prevalent in elders even with milder forms of cognitive impairment in clinic-based (Drijgers *et al.*, 2011) and community-based (Lyketsos *et al.*, 2002; Onyike *et al.*, 2007; Clarke *et al.*, 2010) samples. The results of a study by Oniyke *et al.* (2007) suggest that apathy is an early sign of cognitive decline and that delineating phenotypes in which apathy and a mild cognitive syndrome co-occur may facilitate earlier identification of individuals at risk for dementia. The notion emerges of an MCI plus apathy

phenotype that progresses to dementia (Bruen *et al.*, 2008), and it is also possible that apathy precedes MCI.

It should be also underlined that elders identified as having apathy are more likely than elders who do not have apathy to have impairments in executive domains of cognitive function and be referred for behaviours evoking embarrassment (Ott *et al.*, 1996; Politis *et al.*, 2004). These impairments are reported to increase considerably the burden of caregivers (Landes 2001; Politis *et al.*, 2004). Caregivers also commonly misinterpret the loss of motivation and engagement as a sign of emotional disturbance or oppositional behavior, leading to additional caregiver distress and dissatisfaction with caregiving (Landes *et al.*, 2001). Clinicians should always bear in mind that assessment of apathy is important in identifying which patients and families will require additional support and care.

Apathy and Depression

Apathy and depression may share some clinical features, such as loss of interest, reduced activity or anhedonia (Landes, 2001), but may have a different pathophysiology and treatment (Landes, 2001; Holthoff *et al.*, 2005; Kang *et al.*, 2011). Differentiating among symptoms of depressed mood, apathy, anhedonia, or anergia is sometimes difficult because of the overlap in clinical features (Lavretsky *et al.*, 2008). Clinicians should always bear in mind that these clinical entities may be hard to discern or even coexist (Landes, 2001; Lyketsos, 2007; Robert *et al.*, 2009). When apathy and depression co-occur patients may present with symptoms resistant to treatment as usual and so alternative treatment plans may be in order (Robert *et al.*, 2009).

The underlying mechanisms responsible for apathy

Motivational circuitry of the brain includes such important structures as the nucleus accumbens, ventral pallidum, and ventral tegmental area with projections to the amygdala, hippocampus, basal ganglia, motor cortex, and anterior cingulate. A more profound state of psychomotor retardation and apathy, or abulia can result from strokes that disrupt fronto-subcortical pathways, such as anterior cingulate and capsular lesions (Lavretsky *et al.*, 2007). The concept of apathy is a common feature of prefrontal and basal ganglia lesions or dysfunctions (Mega and Cummings, 1994; Levy and Dubois, 2006). It seems that in patients who present apathy the capacity of the frontal cortex to select, initiate, maintain and shift programs of action is undermined (Levy and Dubois, 2006). Levy and Dubois (2006) propose that the underlying mechanism responsible for apathy is disruption of “emotional-affective” processing probably related to lesions in orbitofrontal cortex and related limbic territory, and/or disruption in “cognitive” processing probably related to lesions in the dorsolateral prefrontal cortex and the related caudate nucleus and/or disruption in “autoactivation” processing probably related to lesions in the associative and limbic areas of globus pallidus.

With regards to dementia Lyketsos proposes that apathy is an aspect of Executive Dysfunction Syndrome (Lyketsos *et al.*, 2004), and is probably caused by damage to frontal-subcortical brain circuits (Craig *et al.*, 1996; Benoit *et al.*, 1999).

Apathy is correlated with neuronal loss, higher tangle counts, and white-matter hyperintensities in areas that are thought to be essential components of these frontal subcortical circuits (Benoit *et al.*, 1999; Robert *et al.*, 2006). Functional imaging studies find that apathy in AD is associated with hypoperfusion in regions that are involved in frontal-subcortical networks. (Craig *et al.*, 1996; Ott *et al.*, 1996; Benoit *et al.*, 1999).

Methods

The method we followed was to identify relevant neuroimaging studies from an extensive electronic search from the databases included in the National Library of Medicine for " apathy and dementia " (926 results), as well as PsychInfo and Google Scholar. Further articles for inclusion were identified by searching the references of retrieved articles and by checking the Cochrane library. Articles that involved patients with dementia other than Alzheimer's Disease or that did not report a specific outcome measure of apathy were excluded. All articles were read in full and their level of evidence and outcome were assessed by all the authors.

Results

With regards to neuroimaging, several studies have tried to identify the brain areas involved with apathy in Alzheimer's Disease (See Table 1). Among these studies ten were conducted with the use of SPECT (Craig *et al.*, 1996; Ott *et al.*, 1996; Benoit *et al.*, 1999, 2002, 2004; Migneco *et al.*, 2001; Tanaka *et al.*, 2004; Robert *et al.*, 2006; David *et al.*, 2008; Kang *et al.*, 2012), five with the use of PET (Lopez *et al.*, 2001; Holthoff *et al.*, 2005; Mega *et al.*, 2005; Marshall *et al.*, 2007; Schroeter *et al.*, 2011), one with combined use of MRI and SPECT (Lanctôt *et al.*, 2007), six with MRI scans (Apostolova *et al.*, 2007; Bruen *et al.*, 2008; Lavretsky *et al.*, 2008; Starkstein *et al.*, 2009b; Jonsson *et al.*, 2010; Tunnard *et al.*, 2011), and three with DTI (Kim *et al.*, 2011; Ota *et al.*, 2012; Tighe *et al.*, 2012). In these studies apathy was evaluated in fifteen of them with the Neuropsychiatric Inventory (NPI) (Craig *et al.*, 1996; Benoit *et al.*, 1999, 2002; Migneco *et al.*, 2001; Tanaka *et al.*, 2004; Mega *et al.*, 2005; Holthoff *et al.*, 2005; Lanctôt *et al.*, 2007; Apostolova *et al.*, 2007; Bruen *et al.*, 2008; Kim *et al.*, 2011; Schroeter *et al.*, 2011; Tunnard *et al.*, 2011; Kang *et al.*, 2012; Tighe *et al.*, 2012), in three with the Apathy inventory (Benoit *et al.*, 2004; Robert *et al.*, 2006; David *et al.*, 2008), in two with the Apathy Scale (Starkstein *et al.*, 2009; Ota *et al.*, 2012), in one (Ott *et al.*, 1996) with the Apathy Evaluation Scale (AES), in one (Lopez *et al.*, 2001) with a semi-structured interview for psychiatric evaluation, in one (Marshall *et al.*, 2007) with the Scale for the Assessment of Negative Symptoms in Alzheimer Disease (SANS-AD), in one (Jonsson *et al.*, 2010) with the Stepwise comparative status analysis (STEP) and finally in one (Lavretsky *et al.*, 2008) with the Psychiatric Evaluation section of the Minimum Uniform Dataset (MUDS) of the California Alzheimer's Disease Centers Program.

Studies with SPECT

In a study by Craig *et al.* (1996) the use of technetium-99m-HMPAO SPECT, within 3 months of administration of the Neuropsychiatric Inventory, in 31 probable AD patients (mean MMSE score 17.6, SD 6.9; range 0–27) indicated that the presence of apathy was

associated with severer prefrontal and anterior temporal dysfunction. These regional cerebral perfusion relationships with apathy were independent of cognitive decline except in the dorsolateral prefrontal cortex. The authors concluded that their findings are consistent with similar ones previously reported in other disorders. In a technetium-99m-HMPAO SPECT study conducted by Ott *et al.* (1996) in 40 possible AD patients (MMSE score 18.5, SD 5.5) the presence of apathy (evaluated with the Apathy Evaluation Scale) was associated with decreased right temporoparietal perfusion. In this study, problem behaviors were highly correlated with apathy and were not with general cognitive impairment as measured by the MMSE. Therefore, the authors suggested that attention to motivation may provide the clinician with a useful indicator of patients who will need close attention to behavior management. Benoit *et al.* (1999) has used NPI to examine 'behavioral and psychological signs and symptoms of dementia' (BPSSD). Sixty-three French patients (mean age 74.7 years, SD 7.9) with a Mini-Mental State Examination (MMSE) score higher than 10 were examined. BPPSD were detected by NPI in 95.2% of the patients. The highest frequency severity NPI score was observed for apathy. Twenty of these AD patients underwent a technetium-99m-bicisate SPECT protocol within the same week as the NPI evaluation. The mean age of this population was 74.4 years (SD 5.3) and the mean MMSE score was 21 (SD 4.1). The apathy NPI score was correlated with right cingulate deficit whereas the highest correlation for the MMSE was with the left temporoparietal area. This study by Benoit underlined the close relationship between apathy and hypoactivity of the cingulate gyrus (Benoit *et al.*, 1999). In the study by Migneco *et al.* (2001) forty-one subjects were studied. According to ICD 10 diagnostic criteria, 28 patients had AD and 13 had organic personality disorders or MCI not attributable to dementia. Apathy was evaluated with the NPI. Patients were divided into two symptomatic subgroups: apathetic or nonapathetic. Brain perfusion was measured by 99mTc-labeled bicisate (ECD) brain SPECT and the images were compared using Statistical Parametric Mapping (SPM96). Twenty-one subjects were apathetic (14 in the demented group and 7 in the non-demented group) and 20 were not apathetic (14 in the demented group and 6 in the non-demented group). The study by Migneco *et al.* (2001) included AD subjects but also patients with other cognitive disorders at the time of evaluation, such as mild cognitive impairment or organic personality disorders and whatever the stratification (whole population, demented subjects only, or nondemented subjects only), the common feature of the apathetic subgroups was always the anterior cingulate hypoperfusion. The authors underline that cingulate hypoperfusion is more anterior in demented than in non-demented apathetic subjects. However, in both cases, hypoperfusion was located in the same region of the cingulate called the cognitive effector region. The aim of the study by Benoit *et al.* (2002) was to evaluate brain perfusion of AD patients with and without apathy (as determined by the NPI) compared with that in healthy elderly subjects. 15 AD patients without apathy (mean age 76.6) and 15 AD patients with apathy (mean age 77.6) were studied. Brain perfusion was measured by 99mTc-labeled bicisate (ECD) single-photon emission tomography (ECD SPECT). The images of the two AD subgroups were compared by means of SPM99 to corresponding images of 11 healthy elderly control subjects. Compared with the healthy elderly subjects, the apathy-free AD subgroup had significantly lower perfusion of inferior temporal regions (left fusiform gyrus, left parahippocampal area) and occipital regions (left gyrus lingualis). The apathy subgroup had significantly decreased perfusion of the left anterior cingulate, the right inferior and

medial gyrus frontalis, the left orbitofrontal gyrus and the right gyrus lingualis. The authors suggested that the differences in the brain areas with reduced perfusion between the apathy-free subjects (mainly the posterior regions) and the apathetic subjects (mainly the anterior regions) indicate that behavioural disorders such as apathy participate in the heterogeneity of brain perfusion in AD. The results confirmed the significant cingulate hypoperfusion in apathetic AD patients compared with healthy control subjects, but not compared with apathy-free AD patients. In the study by Benoit *et al.* (2004) thirty AD patients were included. Lack of initiative, lack of interest and of emotional blunting were assessed with the Apathy Inventory (IA), a tool designed to provide a separate assessment of the behavioral, cognitive and emotional, aspects of apathy. Brain perfusion was measured by 99mTc-labeled bicisate (ECD) single photon emission tomography. The Statistical Parametric Mapping software provided negative correlation between apathy Inventory total score and brain perfusion in left and right superior orbito-frontal gyrus, and to a lesser extent in left middle frontal gyrus (BA10). Lack of initiative score was negatively correlated with perfusion in right anterior cingulate cortex. Lack of interest score was negatively correlated with perfusion in right middle orbitofrontal gyrus. Emotional blunting score correlated negatively with in left superior dorsolateral prefrontal cortex activity. The correlation observed (Benoit *et al.*, 2004) between Apathy Inventory total score and bilateral frontal hypoperfusion confirms previous brain imaging studies in AD which have suggested relationships between apathy and abnormal perfusion in the frontal cortex and in the cingulate area (Craig *et al.*, 1996; Benoit *et al.*, 1999; Migneco *et al.*, 2001). Moreover, anterior cingulate area hypoperfusion is reported to specifically relate apathy regardless of the presence of dementia (Migneco *et al.*, 2001)

It was also demonstrated that, compared with healthy subjects, the apathetic AD patients had significantly decreased perfusion in the anterior cingulate, the inferior and medial gyrus frontalis and the orbitofrontal gyrus (Benoit *et al.*, 2002). Tanaka *et al.* (2004) conducted a study with SPECT (data were analysed with SPM 99) in order to assess the efficacy of donepezil in 70 patients with mild to moderate AD. Among the 21 patients who responded to treatment with donepezil apathy as well as dysphoria and anxiety significantly improved. CBF in the premotor and parietotemporal cortices was significantly higher in the responder group than in the worse group. Robert *et al.* (2006) used single photon emission tomography (SPECT) to measure brain perfusion. Thirty-one AD patients were included. Lack of initiative and interest were assessed with the Apathy Inventory. Nineteen AD subjects presented a lack of initiative and interest pathological score whereas 12 AD subjects did not. The lack of initiative and interest score correlated significantly with altered perfusion in the right frontal and the right inferior temporal lobes. The AD patients with lack of initiative and interest showed a significantly lower perfusion in the right anterior cingulate than the AD patients without lack of initiative and interest. The authors propose that although these results derive from rather small subgroups of patients but have the interest to dismantle the complementary aspects of emotion and motivation in apathy and suggest that the latter one is more related to cingulate area. David *et al.* (2008) used 123I-FP-CIT (DaTSCAN) SPECT in 14 AD patients and 8 patients with dementia with Lewy body. A relationship between apathy and Dopamine transporter (DAT) levels was found independent from motor activity. It was suggested that dementia patients presenting with apathy are characterized by some

degree of striatal dopaminergic neuronal loss. Kang *et al.* (2012) conducted a study with 99mTc-HMPAO SPECT in 81 AD patients. Apathetic non-depressed patients patients had lower perfusion in the right amygdala, temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri than non-apathetic patients. Apathy and depression in AD patients were found to involve distinct functional circuits.

Studies with PET

In a study by Lopez *et al.* (2001) one patient with apathy, who was examined with the use of PET, was found to have diminished rel-CBF in the basal ganglia and dorsolateral prefrontal cortex, bilaterally (Lopez *et al.*, 2001). Apathy was assessed with a semi-structured interview for psychiatric evaluation. Holthoff *et al.* (2005) examined 53 patients with AD (Mini-Mental State Examination (MMSE) 22.5 ±2.94 points). Of all symptoms, apathy and depression were most frequently encountered. The patient group with apathy (n = 17) revealed significantcerebral glucose metabolism decreases in left orbitofrontal regions when compared with patients free of apathy. Depression of clinical significance (n =10) was associated with hypometabolism in dorsolateral prefrontal regions. The authors propose that these findings lend support to the notion that different functional circuits underlie apathy and depression in early AD. According to the authors, in early disease, functional deficits in the specific pathway involved in apathetic symptoms are detectable in orbitofrontal regions first and that dysfunction in additional circuit members becomes apparent as disease progresses or more behavioural symptoms emerge. Mega *et al.*, (2005) conducted a study with Fludeoxyglucose F 18 PET in order to map brain metabolism associated with treatment response to galantamine in 19 patients with mild to moderate AD. Right cingulate metabolic change significantly correlated with improvement in depression and right ventral putamen metabolic change with improvement in apathy ($p \leq 0.05$ for both). In the study by Marshall *et al.*, (2007) forty-one subjects with probable AD underwent [18F] fluorodeoxyglucose positron emission tomography imaging and neuropsychiatric and cognitive assessments. Apathy was assessed with the Global subscale scores from the Scale for the Assessment of Negative Symptoms in Alzheimer Disease (SANS-AD). Twenty-seven (66%) subjects did not have apathy, whereas 14 (34%) had apathy. Statistical parametric mapping analysis revealed reduced significantly metabolic activity in the bilateral anterior cingulate region extending inferiorly to the medial orbitofrontal region ($p \leq 0.001$) and the bilateral medial thalamus ($p = 0.04$) in subjects with apathy. The results of the statistical parametric mapping analysis remained the same after individually co-varying for the effects of global cognitive impairment, depressed mood, and education. The authors propose that the current study extends this distinction to regional brain function and suggests that neurobiologic correlates of apathy in AD are independent of depressed mood and delusional thoughts. Finally, the authors suggest that these results reinforce the confluence of evidence from other investigational modalities in implicating medial frontal dysfunction and related neuronal circuits in the neurobiology of apathy in AD and other neuropsychiatric diseases. In the study by Schroeter *et al.* (2011) FDG- PET data analyzed with Statistical Parametric Mapping (SPM5) were obtained from 54 subjects mainly with early AD, frontotemporal lobar degeneration, and subjective cognitive impairment. Apathy was related to the ventral tegmental area, a component of the motivational dopaminergic network.

Studies with SPECT and MRI

In the study by Lanctot *et al.* (2007), SPECT and MRI scans were obtained from 51 non-depressed outpatients meeting criteria for probable AD (age 77.6 ± 6.6 years; MMSE 22.3 ± 5.1; 23 apathetic, 28 nonapathetic) and 23 healthy elderly (75.6 ± 3.8 years) controls. Relative to nonapathetic AD patients, apathetic AD patients had lower perfusion in 2 ROIs (right orbitofrontal cortex and left anterior cingulate) and higher perfusion in 5 ROIs (right and left hippocampi, left medial superior temporal gyrus, and right and left medial temporal cortex). Comparison of rCBF in these 7 ROIs to those of healthy elderly controls confirmed hypoperfusion in the left anterior cingulate and right orbitofrontal cortex and suggested a relative sparing of perfusion among apathetic AD patients in the remaining 5 ROIs.

Studies with MRI

Apostolova *et al.*(2007) analyzed magnetic resonance imaging data of 35 AD patients with and without apathy. There was a significant linear association between apathy severity and cortical gray matter atrophy in the bilateral anterior cingulate [Brodmann area (BA) 24; $r = 0.39–0.42$, $p = 0.01$] and left medial frontal cortex (BA 8 and 9; $r = 0.4$, $p < 0.02$). Left mean cingulate cortical thinning predicted the presence/absence of apathy at the trend level of significance. The authors propose that their findings demonstrate a strong association between apathy and the integrity of medial frontal regions in AD. Starkstein *et al.* (2009) obtained three-dimensional MRI scans from 79 patients with probable Alzheimer's disease. Patients with apathy showed a significantly larger volume of frontal white matter hyperintensities than patients without apathy. Patients with depression had a significantly larger volume of right parietal white matter hyperintensities than patients without depression. However, neither apathy nor depression was significantly associated with lobar gray or white matter atrophy. The authors propose that frontal and right parietal white matter hyperintensities were the strongest brain structural correlates of apathy and depression in Alzheimer's disease. In the study by Lavretsky *et al.* (2008) 270 community-dwelling older adults underwent MRI and the distribution of cognitive status included: cognitively intact (38%), cognitively impaired (27%), or demented (35%). 41% of the patients were classified as having subcortical lacunes. Depressed mood, anhedonia, anergia, and apathy apparent at the time of assessment were assessed using Psychiatric Evaluation section of the Minimum Uniform Dataset (MUDS) of the California Alzheimer's Disease Centers Program. Subjects with neuropsychiatric symptoms were more likely to be cognitively impaired or demented than those without neuropsychiatric symptoms. In multivariate models controlling for cognitive status, age, gender, and education, higher lacunar volume in white matter was independently associated with the presence of all four neuropsychiatric symptoms. The authors argue for an association between the lacunar volumes in the white matter and depressed mood, anhedonia, apathy, and anergia, thus supporting the role of subcortical ischemic vascular disease in the pathogenesis of late-life neuropsychiatric disorders. Bruen *et al.* (2008) used voxel-based morphometry to correlate gray matter (GM) derived from T1-weighted MRI images of 31 patients with mild Alzheimer's disease and specific neuropsychiatric symptoms and behaviors were assessed with the Neuropsychiatric Inventory. Delusions were associated with decreased GM density in the left frontal lobe, in the right frontoparietal cortex and in the left claustrum. Agitation was associated with

decreased GM values in the left insula, and in anterior cingulate cortex bilaterally. Neuropsychiatric symptoms of Alzheimer's disease seem to associate with neurodegeneration of specific neural networks supporting personal memory, reality monitoring, processing of reward, interoceptive sensations and subjective emotional experience. Apathy was associated with GM density loss in the anterior cingulate and frontal cortex bilaterally, the head of the left caudate nucleus and in bilateral putamen. The authors propose that although Alzheimer's disease research has largely concentrated on the study of cognitive decline, the associated behavioural and neuropsychiatric symptoms are of equal importance in the clinical profile of the disease. Jonsson *et al.*, (2010) conducted a study using CT and MRI scans in 176 patients with AD, vascular dementia, mixed dementia and MCI. Apathy was among the most consistent predicting factors for cerebral white-matter changes. In the study by Tunnard *et al.*, (2011) MRI scans were used to assess 111 mild to moderate AD patients. Apathetic patients had significantly greater cortical thinning in left caudal anterior cingulated cortex (ACC) and left lateral orbitofrontal cortex (OFC), as well as left superior and ventrolateral frontal regions, than those without apathy symptoms.

Studies with DTI

Fifty-one very mild or mild probable AD subjects were assessed with volumetric magnetic resonance imaging and diffusion tensor imaging (Kim *et al.*, 2011). Volume of interest analyses were performed to compare regional fractional anisotropy (FA) between apathy and apathy-free group, and to test a linear relationship between regional FA and apathy severity. Apathy was assessed by the Neuropsychiatric Inventory. Apathy group showed significantly lower FA values than apathy-free group in the left anterior cingulum (A-C), regardless of concomitant depression and psychotropic medications. Left A-C FA values also had significant linear relationship with apathy-composite scores as a measure of apathy severity, even after controlling for gray matter density of the ipsilateral anterior cingulated cortex. The authors suggested that communication failure between the anterior cingulate cortex and other brain structures via the anterior cingulum contributes to the development and aggravation of apathy in AD. In the study by Ota *et al.* (2012), the association between apathy and white matter integrity(FA index) was examined with the use of diffusion tensor imaging (DTI) in twenty-one AD patients in a voxel-based morphometry manner. Apathy was found to be associated with impaired white matter integrity in the anterior cingulated and medial thalamus. The authors proposed that these results lend support to previous investigational findings that implicate limbic dysfunction and related neuronal circuits in the neurobiology of apathy in AD. Finally, in the study by Tighe *et al.* (2012), involving 22 MCI and 23 AD patients, participants within the lowest anterior cingulum (AC) fractional anisotropy tertile were more likely to exhibit irritability, agitation, dysphoria, apathy, and nighttime behavioral disturbances compared to those in the highest tertile. However, in the multivariate model, after adjusting for MMSE, only irritability remained significant.

Discussion

The present neuroimaging findings lend support to the notion that apathy in patients with AD is correlated with alterations in structure and function within distributed frontal-subcortical networks.

Most of the studies described in this review involve the anterior cingulate cortex. The anterior cingulate cortex (Brodmann areas 24, 32) has major reciprocal or afferent connections with the orbitofrontal cortex (Brodmann areas 10, 11, 47), other limbic areas and basal ganglia (Mega et al., 1997). A crucial function of the anterior cingulate cortex relates to the initiation and motivational drivers for goal directed activities, particularly when these are effortful, and damage to this cortical structure would likely, therefore, lead to a degree of behavioural and cognitive inactivity (Allman *et al.*, 2001). Kim and colleagues (2011) found that apathy in AD is associated with microstructural alteration of the *anterior cingulum*, left side in particular, independently of concomitant depression, psychotropic medications, and anterior cingulate cortex Grey Matter changes. They proposed that communication failure between the anterior cingulate cortex and other brain structures via the *anterior cingulum* contributes to the development and aggravation of apathy in AD, supporting the general notion of disconnection syndrome for clinical manifestation of AD.

Orbitofrontal area seems to be another brain area associated with apathy in AD. Wallis (2007) proposed that the orbitofrontal cortex integrates sensory, affective, and motivational information to derive potential reward outcome values in a model study of neuronal mechanisms underlying decision-making in the prefrontal cortex. A recent model by Guimaraes et al. (2008) proposes that the anterior cingulate cortex and the orbitofrontal cortex are part of a broader frontostriatal circuit which is involved in decision-making. Specifically, these regions are proposed to be involved in evaluating action and outcomes and, via the basolateral amygdala and nucleus accumbens, feed into an ascending frontostriatal pathway to the dorsolateral prefrontal cortex, which is responsible for selecting and executing behavioural responses. Damage to the anterior cingulate cortex and orbitofrontal cortex leads to a disruption of this circuit resulting in impaired decision-making and impaired response initiation, which presents as apathy. There is evidence of high levels of apathy subcortical disease, such as Parkinson's Disease, resulting from dysfunction at the striatal level, though Tunnard et al. (2011) with their recent study suggest than in AD the locus of dysfunction is at the cortical level, namely the anterior cingulate cortex and orbitofrontal cortex. However, other researchers (Bonelli and Cummings, 2007) consider that the dysfunction of the orbitofrontal cortex circuit results in disinhibition syndromes while it is the dysfunction of only the anterior cingulate cortex circuit which is responsible for the presentation of apathy. Future neuroimaging studies should aim to elucidate this controversy. Apart these two brain areas, there were reports of hypoactivity in prefrontal, anterior temporal, right temporo-parietal, right inferior and media frontal gyrus, right gyrus lingualis and subcortical structures among others being associated with apathy in AD. The heterogeneity of the results is owed to numerous effects such as the differential neurobiological process that mediates disease features, the stage at the time of study, the individual brain characteristics and factors pertaining to the imaging procedures followed (type of scanner used, data processing workup, results reporting), study design issues, and the apathy measuring method. It is important to note the inherently indirect relationship between the image signal and the neurobiological process being studied, as well as the variable anatomical correspondence for a given imaging modality (e.g., FA in regions of highly crossing white matter tracts).

Apathy seems to be prevalent both in AD and MCI (Cummings *et al.*, 1996; Lyketsos *et al.*, 2000, 2002; Oniyke *et al.*, 2007). It is of great importance to assess and diagnose as sooner as possible apathetic elderly patients within the community since it is proposed that the wider recognition of apathy and its association with mild cognitive syndromes could facilitate earlier diagnosis of dementia (Oniyke *et al.*, 2007). Apart the use of pertinent scales like the Neuropsychiatric Inventory (NPI), the Apathy Evaluation Scale (AES), the Apathy Inventory, the Apathy Scale etc., the generalization of neuroimaging techniques might be able to offer help in this domain. It should be noted that methodological issues such as the degenerative disease state at the time of study, study population and study design, may confound the assessment of apathy. However, statistical differences should be interpreted with caution given the lack of an integrated knowledge about the structures involved as well as the uncertainty whether the changes represent a primary (due to neuropathology) or secondary (due to pathology effects) process. Despite existing evidence, the pathophysiology of apathy has not been clarified yet. Longitudinal imaging data to add means to cross-sectional results and to integrate the understanding of apathy, although at the expense of cost, are lacking. Tracking changes to make disease trajectories, especially in multisite samples, which is also correcting for the individual brain imaging variation, will broaden the existing knowledge, and along with the use of evolving imaging techniques and image analysis tools, should inform neural network models of apathy and its neurodegeneration and psychiatric co-morbidity. Identifying patterns of time-wise quantitative neurobiological information may provide a more solid frame of apathy, and may allow to inferring on various critical issues, namely what is apathy as a distinct syndrome, the association between apathy and neurodegenerative diseases, so to allow predictions, and to test imaging markers for disease and treatments.

Accumulative evidence on the diverse role of anterior cingulate cortex and related cortical structures will inform more sophisticated study designs of apathy with the use of neuroimaging, and multimodal assessment studies are in this line. Furthermore, etiopathological studies applying the modern tools of brain imaging, genetics, and neuropathology (Lyketsos, 2007) should continue examine the brain correlates of apathy.

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TABLE 1

REVIEW OF NEUROIMAGING STUDIES OF APATHY IN ALZHEIMER'S DISEASE

Authors	Method	Scale Apathy	Subjects	Results
Craig *et al.*, 1996	^{99m} Tc-HMPAO SPECT	NPI	31 probable AD patients (MMSE score 17.6, SD 6.9)	More severe prefrontal and anterior temporal hypoperfusion associated with apathy
Ott *et al.*, 1996	^{99m} Tc-HMPAO SPECT	AES	40 possible AD patients (MMSE score 18.5, SD 5.5)	Lower right temporoparietal perfusion correlated with apathy
Benoit *et al.*, 1999	^{99m} Tc-ECD SPECT…(bicisate)	NPI	20 AD patients (MMSE score 21, SD 4.1)	Hypoactivity (hypoperfusion) of the cingulate gyrus.
Migneco *et al.*, 2001	^{99m} Tc-ECD SPECT	NPI	28 ICD-10 AD patients (MMSE 20 SD 3.8) and 13 subjects with organic personality disorders or MCI (MMSE 22.2 SD 3.4)	Hypoactivity (hypoperfusion) of anterior cingulate region
Lopez *et al.*, 2001	PET	Semi- structured interview for psychiatric evaluation	1 AD pt with major depression (MMSE 20), 1 AD pt with emotional lability (MMSE 24), 1 AD pt with apathy (MMSE 19) 5 non–mood disordered AD pts (MMSE 20.4±4.6) 9 non-demented controls	The patient with apathy had diminished relative CBF in the basal ganglia and the dorsolateral prefrontal cortex, bilaterally.
Benoit *et al.*, 2002	^{99m} Tc-ECD SPECT and SPM99	NPI	15 AD patients with apathy (MMSE 19.8 SD 3.7) 15 AD patients without apathy(MMSE 22.2 SD 3.3) 11 Healthy controls	Decreased perfusion of left anterior cingulate, right inferior and medial gyrus frontalis, left orbitofrontal gyrus and right gyrus lingualis was found in the apathetic subgroup
Benoit *et al.*, 2004	^{99m} Tc-ECD SPECT and SPM99	Apathy Inventory (IA)	30 AD patients MMSE 22.3	Negative correlation between IA total score and brain perfusion in left and right superior orbito-frontal gyrus, and to a lesser extent in left middle frontal gyrus (BA10). Lack of initiative score correlated with hypo-perfusion in right anterior cingulate cortex. Lack of interest score correlated with hypo- perfusion in right middle orbitofrontal gyrus. Emotional blunting score correlated with hypoperfusion in left superior dorsolateral prefrontal cortex
Tanaka *et al.*, 2004	SPECT data analyzed by SPM99	NPI	70 patients with mild to moderate AD	21 patients showed a behavioral response, 42 showed no behavioral change and 7 worsened after treatment with donepezil. Dysphoria, anxiety and apathy significantly improved among the responder group. CBF in the premotor and parietotemporal cortices was

				significantly higher in the responder group than in the worse group.
Mega *et al.*, 2005	[^{18}F]FDG-PET To map brain glucose metabolism changes associated with treatment response to galantamine	NPI	19 patients with mild to moderate AD	Right cingulate glucose metabolism change significantly correlated with improvement in depression and right ventral putamen metabolic change correlated with improvement in apathy ($p \leq 0.05$ for both).
Holthoff *et al.*, 2005	PET	NPI	53 AD patients (MMSE 22.5 SD 2.94) 17 with apathy	Hypometabolism of left orbitofrontal cortex
Robert *et al.*, 2006	SPECT	Apathy Inventory	Thirty AD patients (MMSE 22.8 SD 3)	Lack of initiative and lack of interest were associated with hypoperfusion in right anterior cingulate
Marshall *et al.*, 2007	[^{18}F]FDG-PET	Scale for the Assessment of Negative Symptoms in Alzheimer Disease SANS-AD	14 AD patients with apathy (MMSE 16.8 SD 5),27 AD patients without apathy (MMSE 21.1 SD 6.2)	Reduced glucose metabolism in anterior cingulate cortex, medial orbitofrontal region and bilateral medial thalamus was found in the apathetic group
Lanctôt *et al.*, 2007	SPECT and MRI scans	NPI	51 non- depressed patients with probable AD (MMSE 22.3 SD5.1) 23 apathetic, 28 non-apathetic, 23 healthy matched controls	Lower perfusion rates in right orbitofrontal cortex and left anterior cingulated were estimated in the apathetic group
Apostolova *et al.*, 2007	MRI	NPI	35 AD patients	Greater cortical gray matter atrophy in the bilateral anterior cingulate and left medial frontal cortex correlated with apathy
Starkstein *et al.*, 2009	MRI	APATHY SCALE	79 probable AD patients	Frontal white matter hyperintensity burden associated apathy
Lavretsky *et al.*, 2008	MRI	Psychiatric Evaluation section of the Minimum Uniform Dataset (MUDS) of the California Alzheimer's Disease Centers Program	270 community dwelling elderly cognitively intact(38%), cognitively impaired (27%), demented (35%)	Apathy was associated with higher total volume of lacunes in the white matter
Bruen *et al.*, 2008	MRI and voxel- based morphometry	NPI	31 mild AD patients	GM density loss in the anterior cingulate and frontal cortex bilaterally, the head of the left caudate nucleus and in bilateral putamen was associated with apathy
David *et al.*, 2008	^{123}I-FP-CIT SPECT (DaTSCAN)	Apathy Inventory (IA)	14 AD patients 8 patients with dementia with Lewy body	A relationship between apathy and Dopamine transporter (DAT) levels was found to be independent from motor activity. It was suggested that dementia patients presenting with apathy are characterized by some degree of dopaminergic neuronal loss.
Jonsson *et al.*, 2010	CT and MRI	Stepwise comparative status analysis (STEP)	176 patients with AD, vascular dementia, mixed… dementia and MCI	Apathy was among the most consistent predicting factors for cerebral white-matter changes.
Kim *et al.*, 2011	volumetric MRI with diffusion tensor imaging (DTI)	NPI	51 very mild or mild probable AD subjects	Apathy group showed significantly lower fractional

				anisotropy (FA) values than apathy-free group in the left anterior cingulum (A-C). Left A-C FA values also had significant linear relationship with apathy-composite scores as a measure of apathy severity
Schroeter *et al.*, 2011	[^{18}F]FDG-PET with Statistical Parametric Mapping (SPM5)	NPI	54 subjects mainly with early AD, frontotemporal lobar degeneration, and subjective cognitive impairment	Apathy was associated with hypometabolism in the ventral tegmental area, a component of the motivational dopaminergic network
Tunnard *et al.*, 2011	MRI	NPI	111 mild to moderate AD patients	Apathetic patients had significantly greater cortical thinning in left caudal anterior cingulate cortex (ACC) and left lateral orbitofrontal cortex (OFC), as well as in left superior and ventrolateral frontal regions, than those without apathy symptoms.
Kang *et al.*, 2012	^{99m} Tc-HMPAO SPECT	NPI	81 AD patients	Apathetic non-depressed patients had lower regional perfusion in the right amygdala, temporal, posterior cingulate, right superior frontal, postcentral, and left superior temporal gyri than non-apathetic patients. Apathy and depression in AD patients involved distinct functional circuits.
Ota *et al.*, 2012	MRI with diffusion tensor imaging (DTI)	APATHY SCALE	21 probable AD patients	Apathy was associated with lower white matter integrity index (FA) in the anterior cingulated and medial thalamus.
Tighe *et al.*, 2012	MRI with diffusion tensor imaging (DTI)	NPI	22 MCI and 23 AD participants	Participants within the lowest anterior cingulum (AC) fractional anisotropy tertile were more likely to exhibit irritability, agitation, dysphoria, apathy, and nighttime behavioral disturbances compared to those in the highest tertile. However, only irritability remained significant after adjusting for MMSE.

^{99m}Tc-HMPAO SPECT, (Technetium-99m)-hexamethyl-propylene-aminoxime single-photon emission computed tomography; ECD, ethyl cysteinate dimer; [^{18}F]FDG-PET, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography; ^{123}I-FP-CIT, (Iodine-123)-fluoropropyl-carbomethoxy-iodophenyl-tropane (^{123}I-Ioflupane); MRI, magnetic resonance imaging; NPI, neuropsychiatric inventory; AES, apathy evaluation scale; MMSE, mini- mental state examination; AD, Alzheimer disease; MCI, mild cognitive impairment.