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A SPECT Study of Apathy in Alzheimer's Disease

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Key Words
Alzheimer's disease · Apathy · Single-photon emission tomography

Abstract
Background/Aims: To assess the association between regional cerebral blood flow (rCBF) and apathy in Alzheimer's Disease (AD). ***Methods:*** SPECT and MRI scans were obtained from 51 nondepressed 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. The following regions of interest (ROIs) were compared between apathetic and nonapathetic AD patients and then referenced against aged controls: anterior cingulate, orbitofrontal cortex, middle medial temporal cortex, hippocampus, medial superior temporal cortex, thalamus/hypothalamus and pons. ***Results:*** Apathetic and nonapathetic patients had significant differences in rCBF. 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 middle medial temporal cortex). Comparison of rCBF in these 7 ROIs to 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. ***Conclusions:*** In this group of nondepressed patients with AD, apathetic subjects displayed significant perfusion differences compared to nonapathetic subjects.

Introduction

Apathy has been defined as a lack of motivation and self-initiated action not resulting from an intellectual deficit, a decreased level of consciousness or emotional distress [1, 2]. Apathy has recently been differentiated from depressive symptoms in Alzheimer's disease (AD) [3, 4]. It is a common problem, affecting 36–42% of mildly demented patients and up to 80% of moderately impaired patients [5–8]. Deficits in motivated behaviour lead to functional impairment in basic activities of daily living, such as dressing, bathing and eating, in the affected individual [9]. The result is greater patient reliance on their caregivers for activities of daily living [10, 11] and increased caregiver burden and distress [12, 13]. Apathy has been identified as the primary cause of distress and

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frustration for 65% of caregivers [12, 14] and may increase the risk of patient institutionalization [15, 16].

Data from previous single-photon emission computerized tomography (SPECT) studies have mainly supported the role of the anterior cingulate [17–20] and orbitofrontal regions [17, 20–23]. Associations with temporal regions [17, 20, 24] have been described inconsistently [22, 23]. Some of these studies [17, 19–24] did not exclude AD patients with depressive symptoms, though apathy commonly coexists with depression [10, 16, 25–28]. The presence of depressive symptoms is particularly germane as both anterior cingulate hypoperfusion [29] and diminished metabolism in bilateral superior frontal lobes [30] have been associated with depressive symptoms in AD patients. The inclusion of patients with mild apathy in nonapathetic control groups may also be a confounder in some previous neuroimaging findings [17, 19, 22]. Our objective was to contribute to the literature surrounding the blood flow correlates of apathy associated with AD in patients without significant depressive symptoms.

Materials and Methods

Participants

AD participants were community-dwelling outpatients of either gender aged >55 years evaluated in the Sunnybrook Dementia Study, in which patients, recruited from a university memory clinic, undergo SPECT, magnetic resonance imaging (MRI) scans and neuropsychological testing (within 3 months of scanning). Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [31] and Mattis Dementia Rating Scale [32], as well as several standardized tests of different cognitive domains, functional status was evaluated with the Disability Assessment for Dementia [33] and the Neuropsychiatric Inventory (NPI) [34] was used to assess behaviour. All subjects met the diagnostic criteria of the Diagnostic and Statistical Manual for primary degenerative dementia [35] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for probable AD [36]. Subjects had no evidence of depressive symptoms on the NPI (depression subscore = 0) and were characterized as apathetic (NPI apathy subscale score ≥1) or nonapathetic (NPI apathy subscale score = 0).

In order to establish whether the observed changes in perfusion were a result of AD alone or more specifically related to apathy in AD, healthy elderly controls were recruited from the community by way of local advertisements. Control participants were aged >55 years, displayed no cognitive impairment (MMSE ≥26) at screening, had no significant medical illness, no depressive symptoms (Geriatric Depression Rating Scale [37] <11) and no premorbid or current psychiatric diagnosis (i.e. major mood, psychotic and substance abuse disorders). Neuropsychological testing in the controls confirmed that learning and memory, language, visuospatial function and executive function were within normal limits.

After a complete description of the study, written informed consent was obtained from all participants.

SPECT Imaging and Regional Blood Perfusion Ratios

Subjects received an intravenous injection of 740 MBq of ^{99m}Technetium-labelled L,L-ethyl cysteinate dimer. After 1 h, 120 planar views were collected over 360° using a 3-headed gamma camera (Prism 3000 XP, Picker; Cleveland, Ohio, USA), outfitted with low-energy ultra-high resolution fan beam collimators (focus = 50 cm). Each view was comprised of a 128 × 128 pixel image with a reconstructed image resolution of ~10.5 mm full width at half maximum. Reconstruction of the scans was performed using a ramp-filtered back-projection algorithm (ramp and Butterworth filter with a power of 15 and a cut-off frequency of 0.4 cm^{-1}, and an attenuation correction of $\mu = 0.12\ cm^{-1}$), which was then followed by the use of a 3-dimensional low-pass post-filter (Wiener filter, multiplier 1.0). This produced a spatial resolution of 9.7 mm on the reconstructed scans. After scan acquisition, each SPECT scan was corrected for motion using manufacturer-supplied software, which compensated for frame-to-frame translational shifts. In addition, following reconstruction, images were re-oriented to compensate for overall head tilt in the transverse, sagittal and coronal planes. This adjustment standardizes the slice orientation of the series of SPECT data amongst patients.

Regions of Interest

The reconstructed SPECT scans of the patients were co-registered to a standardized SPECT template of a healthy elderly control, and anatomically-guided regions of interest (ROIs) were then mapped onto the scans [38]. Thirteen ROIs were selected a priori based on previous literature: (1) the anterior cingulate (left and right) [17–20, 39–41]; (2) the prefrontal cortex (left and right) [17, 20–23, 41–43]; (3) the middle medial temporal cortex (contains the amygdala; left and right) [17, 20, 24, 41, 42, 44]; (4) the hippocampus (left and right) [42, 44–46]; (5) the pons (includes the ventral tegmental area) [42, 44–46]; (6) the medial superior temporal gyrus (contains the nucleus accumbens; left and right) [42, 44–46], and (7) the thalamus/hypothalamus (left and right) [42]. The volumes of the anterior cingulate ROIs were 12.29 cm^3 (right) and 11.65 cm^3 (left) and combined the dorsal [Brodmann area (BA) 25], middle (BA 24/32/33) and ventral regions (BA 24/32/33) of the anterior cingulate [38]. The volumes of the orbitofrontal cortex ROIs were 24.9 cm^3 (right) and 25.69 cm^3 (left) and included the frontal poles (BA 10) and orbitofrontal gyri (BA 11). The volumes of the hippocampal area ROIs were 2.71 cm^3 (right) and 2.49 cm^3 (left) (BA 35). The volumes of the middle medial temporal ROIs were 13.58 cm^3 (right) and 13.46 cm^3 (left) and included the parahippocampus, perirhinal cortex and amygdala (BA 28/35/36). The volumes of the superior temporal gyrus, medial portion ROIs were 2.25 cm^3 (right) and 1.90 cm^3 (left) and included the nucleus accumbens as well as the entorhinal cortex and subiculum (BA 27/34). The volume of the pons ROI was 18.02 cm^3 and this ROI included the ventral tegmental area. The volumes of the hypothalamic/thalamic ROIs were 10.73 cm^3 (right) and 10.75 cm^3 (left). ROI data derived from the scans were standardized by first calculating the mean counts per pixel in the chosen regions and then dividing these regional mean counts by the mean counts per pixel in the bilateral lobes of the cerebellum [38]. The cerebel-

lum was chosen as the reference region because blood perfusion in the cerebellum remains fairly unaffected in AD, even as the disease progresses [47] and uptake of ^{99m}Technetium-labelled L,L-ethyl cysteinate dimer has been demonstrated to be approximately proportional to regional cerebral blood flow (rCBF) [48]. Semiquantitative rCBF ratios were obtained from this method and subsequently used for data analysis.

Statistical Analysis

Statistical analyses were done with SPSS© (version 14.0) and all analyses were 2-tailed. To establish comparability of the groups, apathetic and nonapathetic groups were compared on demographic variables using t tests or χ^2 tests as appropriate. Next, to test our hypothesis, rCBF values from apathetic and nonapathetic AD patients were compared using multivariate analysis of variance (MANOVA) with rCBF from the 13 ROIs [orbitofrontal cortices (L, R), anterior cingulate (L, R), thalamus/hypothalamus (L, R), medial superior temporal gyrus (L, R), middle medial temporal cortices (L, R), hippocampus (L, R) and pons] as dependent variables and apathy symptoms (apathetic versus nonapathetic) as the fixed (between-subjects) variable. Post hoc tests were used to determine the contribution of each ROI to the overall difference corrected for multiple comparisons. Next, Spearman rank ρ correlations were used to explore the relationship between the severity of apathetic behaviour and perfusion ratios in both patient groups. In addition, a backward linear regression using forced entry, then stepwise removal of the least significant variables was carried out to detect independent predictors of NPI apathy subscore. In order to determine whether the observed differences between apathetic and nonapathetic patients were specific to apathy or related to AD pathology itself, a secondary MANOVA was performed comparing the apathetic AD patients, nonapathetic AD patients and healthy elderly controls on rCBF values in those ROIs that were found to be significantly related to perfusion differences in the apathetic versus nonapathetic comparison.

Results

Demographics

Of 51 AD patients recruited, 23 were apathetic (range of NPI apathy subscores 1–12) and 28 were nonapathetic (NPI apathy subscore = 0). Apathetic and nonapathetic patient groups were comparable for age, gender distribution and severity of cognitive impairment (as measured by the MMSE and Mattis Dementia Rating Scale; table 1). Despite statistical nonsignificance, there was a trend for apathetic patients to have a lower MMSE and this variable was included as a covariate in subanalyses. While the NPI total score was higher in the apathetic group, there were no significant differences in behaviours characterized on the NPI other than apathy. Thirty-three AD patients were taking psychotropics at the time of the study, including 33 on cholinesterase inhibitors, 12 on antidepressants, 4 on benzodiazepines and 2 on antipsychotics. The proportion of patients taking any psychotropic, or any of the above classes of psychotropics, was not different in apathetic and nonapathetic patients (Fisher exact, all $p > 0.05$).

Table 1. Baseline demographic characteristics

Measure	Apathetic (n = 23)	Nonapathetic (n = 28)	p value
Age, years	76.7 ± 10.0	76.2 ± 7.8	0.86
Gender	15 M/9 F	17 M/12 F	0.77
MMSE	20.7 ± 5.9	23.4 ± 3.9	0.06
DAD total score, %	70.4 ± 23.0	86.8 ± 14.8	0.005[1]
DRS total score	113.5 ± 19.3	119.7 ± 12.7	0.17
NPI total score	12.4 ± 9.5	5.7 ± 7.9	0.007[1]
NPI apathy	4.3 ± 3.3	0	<0.001[1]
NPI depression	0	0	

All data are means ± SD. DAD = Disability Assessment for Dementia; DRS = Mattis Dementia Rating Scale.

[1] Significant p values. p values adjusted for unequal variances if necessary.

SPECT scans were collected from 23 healthy elderly controls. Healthy controls had few depressive symptoms (mean Geriatric Depression Scale 2.9 ± 3.9, all scores <11). Elderly control participants were matched to AD patients on both age (75.6 ± 3.8 years, $t_{72} = -1.37$ $p = 0.18$) and gender (52% male, $\chi^2 = 0.48$, $p = 0.49$).

rCBF and Apathy in AD

MANOVA revealed a significant group effect (apathetic vs. nonapathetic) on the rCBF values measured in 13 ROIs ($F_{13, 37} = 2.89$; $p = 0.006$). Post hoc tests evaluating between-subject effects showed that rCBF values of apathetic patients were significantly lower than nonapathetic patients in the right orbitofrontal cortex and left anterior cingulate. Apathetic patients also displayed significantly greater rCBF than nonapathetic patients in the right and left hippocampi, left medial superior temporal gyrus and right and left middle medial temporal gyri (table 2). There were no significant between-subject effects for rCBF values in any other ROIs. When MMSE was included as a covariate, it was not significant in the overall model ($F_{13, 36} = 1.74$, $p = 0.093$) and the significance of the effect of apathy on rCBF in each individual ROI, with the exception of the left middle medial temporal gyrus, did not change.

Spearman correlations within the AD patient groups indicated that NPI apathy subscore was negatively cor-

Table 2. Comparison of rCBF ratios in ROIs for apathetic (n = 23) and nonapathetic (n = 28) AD patients and healthy elderly controls (n = 23)

ROI hemisphere	AD patients			rCBF control
	rCBF apathetic	rCBF non-apathetic	p value[1]	
Orbitofrontal cortex				
Right	0.72 ± 0.19	0.83 ± 0.06	0.004[2]	0.86 ± 0.06
Left	0.82 ± 0.07	0.83 ± 0.09	0.445	0.86 ± 0.07
Anterior cingulate				
Right	0.71 ± 0.06	0.72 ± 0.09	0.538	0.74 ± 0.05
Left	0.72 ± 0.11	0.79 ± 0.10	0.019[2]	0.82 ± 0.06
Thalamus/hypothalamus				
Right	0.72 ± 0.06	0.71 ± 0.07	0.373	0.77 ± 0.08
Left	0.67 ± 0.07	0.68 ± 0.08	0.799	0.74 ± 0.09
Medial superior temporal gyrus				
Right	0.69 ± 0.08	0.69 ± 0.07	0.875	0.73 ± 0.08
Left	0.72 ± 0.15	0.64 ± 0.07	0.019[2]	0.66 ± 0.06
Middle medial temporal gyrus				
Right	0.64 ± 0.07	0.59 ± 0.08	0.042[2]	0.69 ± 0.08
Left	0.70 ± 0.10	0.65 ± 0.08	0.049[2]	0.73 ± 0.08
Hippocampus				
Right	0.66 ± 0.14	0.53 ± 0.07	<0.001[2]	0.60 ± 0.08
Left	0.61 ± 0.11	0.54 ± 0.09	0.017[2]	0.61 ± 0.09
Pons				
N/A	0.65 ± 0.06	0.65 ± 0.05	0.875	0.67 ± 0.05

All means ± SD.
[1] Between-subject effects from corrected model using MANOVA comparing apathetic and nonapathetic AD patients.
[2] Significant p value.

Table 3. Correlations between rCBF ratios in ROIs and apathy score on the NPI for 51 patients

ROI	Hemisphere	ρ	p value
Orbitofrontal cortex	right	–0.29	0.04[1]
	left	–0.05	0.72
Anterior cingulate	right	–0.14	0.34
	left	–0.39	0.005[1]
Thalamus/hypothalamus	right	0.08	0.58
	left	–0.12	0.42
Medial superior temporal gyrus	right	–0.10	0.49
	left	0.27	0.06
Middle medial temporal gyrus	right	0.26	0.07
	left	0.33	0.02[1]
Hippocampus	right	0.43	0.002[1]
	left	0.27	0.06
Pons	N/A	–0.01	0.92

[1] Significant p value using Spearman rank ρ.

related with regional perfusion ratios in the left anterior cingulate and right orbitofrontal cortices, and positively correlated with regional perfusion ratios in the right hippocampus and left medial superior temporal gyrus. Correlation coefficients and corresponding p values are displayed in table 3. NPI apathy score was also significantly correlated with MMSE (ρ = –0.30; p = 0.035).

Predictors of NPI Apathy Subscore

Linear regression analysis (stepwise, backward entry method), including apathetic and nonapathetic AD patients, where NPI apathy subscore was the dependent variable and rCBF in the significantly correlated ROIs (table 3) and MMSE were independent variables, revealed that spared perfusion in the right hippocampus was an independent predictor of NPI apathy subscore ($F_{1, 49}$ = 9.55, p = 0.003, R^2 = 0.15). All other variables were removed from the final model.

rCBF – AD versus Controls

A secondary MANOVA evaluating rCBF in the ROIs found to be significantly related to apathy in the primary analysis (right orbitofrontal cortex, left anterior cingulate, right and left hippocampi, left medial superior temporal gyrus and right and left middle medial temporal gyri) confirmed group differences ($F_{14, 132}$ = 3.31, p < 0.001). For between-group differences, apathetic AD patients displayed hypoperfusion relative to both nonapathetic AD patients and healthy controls in the right orbitofrontal cortex (p = 0.003) and left anterior cingulate (p = 0.012). In contrast, while apathetic patients displayed increased perfusion relative to nonapathetic patients in the left (p = 0.032) and right (p < 0.001) hippocampi and left medial superior temporal gyrus (p = 0.019), perfusion to these regions in apathetic patients was not significantly different from controls, suggesting that apathy is associated with a sparing of perfusion to these regions. Similarly, while nonapathetic patients displayed significantly reduced perfusion to both the left (p = 0.005) and right (p = 0.0001) middle medial temporal gyri in comparison to healthy elderly controls, rCBF was not significantly reduced in apathetic AD patients. As summarized in figure 1 and table 2, although perfusion to several regions was increased in apathetic versus nonapathetic AD patients in the primary analysis, it was not significantly different from that of healthy elderly controls, suggesting relative and selective sparing of perfusion in apathy associated with AD.

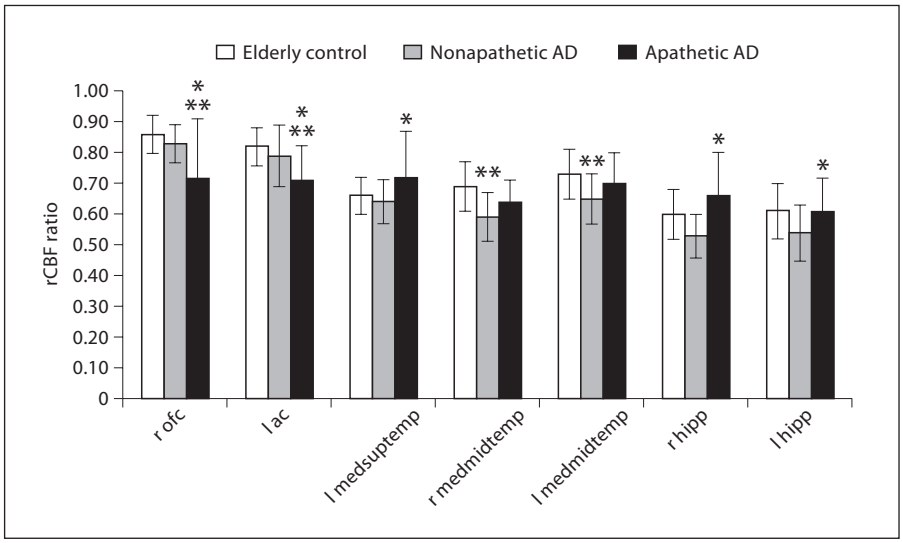

Fig. 1. Comparison of rCBF in apathetic and nonapathetic AD patients and healthy elderly participants in 7 ROIs. r ofc = Right orbitofrontal cortex; l ac = left anterior cingulate cortex; l medsuptemp = left medial superior temporal cortex; r medmidtemp = right medial middle temporal cortex; l medmidtemp = left medial middle temporal cortex; r hipp = right hippocampus; l hipp = left hippocampus. * Significantly different from nonapathetic; ** significantly different from controls. Based on pairwise post hoc Tukey HSD comparisons.

Discussion

This study indicated that there were significant differences in rCBF between nondepressed apathetic and nonapathetic AD subjects. In particular, apathetic AD patients displayed relative hypoperfusion in the right orbitofrontal cortex (BA 10/11) and left anterior cingulate (BA 24/25/32/33) compared to both nonapathetic patients and healthy controls. While apathetic participants had greater perfusion in the hippocampi, middle medial temporal gyri and left medial superior temporal gyrus when compared with nonapathetic participants, rCBF in apathetic AD patients was similar to that found in elderly controls, indicating a relative sparing of these regions. In particular, maintenance of perfusion in the right hippocampus emerged as an independent predictor of severity of apathy symptoms. Strengths of this study were that participants had no depressive symptoms, the nonapathetic group had no symptoms of apathy, the apathetic group had a good range of symptom severity from mild to severe apathy, and the apathetic and nonapathetic groups were comparable for cognitive impairment and the presence of other behavioural and psychological symptoms of dementia. In addition, the AD sample was relatively large and a group of aged-matched normal controls was used for comparison. However, patients participating in our study were not free from psychotropic medications. While the possible impact of medications on perfusion cannot be excluded, the proportions of apathetic and nonapathetic patients taking psychiatric medications were similar.

Hypoperfusion in the left anterior cingulate, as demonstrated in this study, is consistent with the putative role of the anterior cingulate in behaviour. Apathy is the hallmark behaviour in patients with lesions to the anterior cingulate [49] and those affected by disorders that involve injury to the subcortical connections of the anterior cingulate circuit, such as Parkinson's disease [50], Huntington's disease [51] and thalamic lesions [52]. In normal controls, the anterior cingulate is thought to be involved in reward-based decision-making [39]. In AD, hypoperfusion of the anterior cingulate has consistently emerged as a correlate of apathy [3, 17, 19, 20, 22, 23], with previous studies finding bilateral [17, 19], predominantly left [20, 22] and predominantly right [18, 23] hypoperfusion. A previous FDG-PET study in AD suggested that decreased metabolism in the right anterior cingulate was associated with depression [53]. Similarly, a previous SPECT study in AD found that apathy was significantly correlated with reduced left anterior cingulate perfusion independent of depressive symptoms [20]. Thus, right-sided anterior cingulate hypoperfusion found in other studies may reflect the presence of depressive symptoms rather than apathy per se. Our findings suggest that apathy is associated more closely with predominantly left, rather than right, anterior cingulate hypoperfusion.

This study also found a relationship between hypoperfusion in the right orbitofrontal cortex and apathy in AD. Our findings are consistent with other studies reporting hypoperfusion on SPECT [17, 20, 22, 23] and hypometabolism on FDG-PET [54] in the orbitofrontal cortices of apathetic compared to nonapathetic AD patients.

There has been no clear picture of laterality. The FDG-PET study [54] reported decreased orbitofrontal metabolism bilaterally that only reached significance on the left, and the SPECT studies reported hypoperfusion of the right [20, 23] and bilateral [17, 22, 23] orbitofrontal cortices, with some evidence that right-sided orbitofrontal hypoperfusion may be more specifically related to diminished goal-directed cognition [23]. Hypoperfusion in the right orbitofrontal cortex is thought to reflect the dominant role of the right hemisphere in determining affective valence [23]. Medial orbitofrontal cortex hypoperfusion, particularly on the left, is a common feature of depression, being found in patients with primary depression [55] and secondary depression with Parkinson's disease [56], Huntington's disease [57], caudate stroke [58] or complex partial seizures [59], relative to nondepressed comparison groups with the same disorders. Our results suggest that right orbitofrontal hypoperfusion is related to symptoms of apathy in AD.

Importantly, in addition to hypoperfusion in the orbitofrontal cortex and anterior cingulate ROIs, apathetic patients showed relative sparing of the hippocampi (BA 35), middle medial temporal gyri (BA 28/35/36) and left medial superior temporal gyrus (BA 27/34). These ROIs, together with the orbitofrontal and anterior cingulate cortices, are crucial parts of the brain reward system. The neurons that comprise the brain reward system, a vital modulator of motivated behaviours [14], originate in the ventral tegmental area and project axons to key components of the limbic system, including the amygdala, nucleus accumbens and hippocampus [46]. Projections from the ventral tegmental area and nucleus accumbens to the prefrontal cortex and from the prefrontal cortex back to the nucleus accumbens integrate activity of the prefrontal cortex into the circuits involved in motivation [60, 61]. The anterior cingulate has extensive projections to the amygdala, ventral striatum and the nucleus accumbens, and this circuit is important for goal-directed and motivated behaviours [44]. In fact, improved apathy following cholinesterase inhibitor treatment has been associated with activation of the ventral striatum [53]. The orbitofrontal cortex is involved with dopaminergic-mediated reward [41, 62] and pleasure [63] and appears to determine the motivational value of goal-directed behaviour [64]. Thus, apathy may be associated with an imbalance in activity in the brain regions implicated in motivation and reward, which has potential implications for treatments that might regulate the brain reward system such as dopamine agonists and psychostimulants.

In summary, we demonstrated that mild to severe apathy was associated with hypoperfusion in the right orbitofrontal cortex and left anterior cingulate. Interestingly, other ROIs (hippocampi, middle medial temporal gyri, left medial superior temporal gyrus) maintained blood flow similar to that found in aged controls. These results suggest that selective and discreet changes in regional blood perfusion may contribute to apathy in AD patients.

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