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Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study

Julien Delrieu¹, Thomas Desmidt², Vincent Camus², Sandrine Sourdet¹, Claire Boutoleau-Bretonnière³, Emmanuel Mullin⁴, Bruno Vellas^{1,5}, Pierre Payoux^{6,7}, Thibaud Lebouvier³ and Alzheimer's Disease Neuroimaging Initiative[†]

¹Alzheimer's Disease Clinical Research Centre, Gérontopôle, Toulouse University Hospital, Toulouse, France

²CM2R, CHU de Tours, Tours, France

³CM2R, CHU de Nantes, Nantes, France

⁴CM2R, CHU de Nice, Nice, France

⁵UMR1027 INSERM, Université de Toulouse, Toulouse, France

⁶Department of Nuclear Medicine, Toulouse University Hospital, Toulouse, France

⁷UMR825 INSERM, Université de Toulouse, Toulouse, France

Correspondence to: J. Delrieu, E-mail: delrieu.j@chu-toulouse.fr

[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Objective: The goal of this study is to evaluate brain metabolism in mild cognitive impairment (MCI) patients with and without apathy (as determined by the Neuropsychiatric Inventory Questionnaire).

Methods: Baseline data from 65 MCI participants (11 with apathy and 54 without) from the Alzheimer's Disease (AD) Neuroimaging Initiative study were analyzed. All participants underwent a comprehensive cognitive and neuropsychiatric assessment, volumetric MRI and measures of cerebral glucose metabolism applying ¹⁸F-fluorodeoxyglucose positron emission tomography at baseline. The presence of apathy at baseline was determined by the Neuropsychiatric Inventory Questionnaire.

Results: There was no difference between apathy and apathy-free MCI patients regarding cognitive assessment and neuropsychiatric measures when apathy-specific items were removed. Cerebrovascular disease load and cerebral atrophy were equivalent in both groups. Compared with the apathy-free MCI patients, MCI patients with apathy had significantly decreased metabolism in the posterior cingulate cortex.

Conclusion: The presence of apathy in MCI patients is associated with AD-specific pattern of brain metabolic defect. These results could suggest that apathy belongs to the spectrum of prodromal AD symptoms. Copyright © 2014 John Wiley & Sons, Ltd.

Key words: apathy; FDG-PET; biomarker; Alzheimer's disease; mild cognitive impairment; Alzheimer's disease neuroimaging initiative (ADNI)

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Introduction

Apathy and depression are the most frequent neuropsychiatric features in mild cognitive impairment (MCI) (Feldman *et al.*, 2004; Gabryelewicz *et al.*, 2004; Lopez *et al.*, 2005). Differentiating apathy from depression can be challenging as lack of motivation is one of the clinical dimensions of major depression (Starkstein and Leentjens, 2008). However, in

Alzheimer's disease (AD), there are strong arguments to consider that depression and apathy are independent clinical dimensions (Aalten *et al.*, 2007; Aalten *et al.*, 2008). Depression is a well-characterized mental disorder with validated clinical diagnostic criteria and specific validated clinical rating scales (Gelenberg, 2010; Nutt, 2011), but there is still inconsistent evidence that depression increases the conversion rate to dementia in MCI (Panza *et al.*, 2008; Caracciolo *et al.*, 2011;

Chan *et al.*, 2011) (reviewed in the work of Enache *et al.* (2011)). Conversely, apathy remains an ill-defined entity and whether it can exist as an independent psychiatric condition remains an open question (Starkstein and Leentjens, 2008; Drijgers *et al.*, 2010). Yet apathy is a powerful risk factor for conversion to dementia in MCI (Robert *et al.*, 2006b; Teng *et al.*, 2007; Robert *et al.*, 2008), particularly when occurring at the stage of pre-MCI (Duara *et al.*, 2011). When compared with depression, apathy is a better predictor of conversion to dementia (Vicini Chilovi *et al.*, 2009; Palmer *et al.*, 2010). However, available data on apathy remain to the stage of clinical assessment without being corroborated by neuroimaging studies.

In recent years, newly proposed diagnostic criteria for AD have emphasized that the pathological process and its clinical manifestations begin well before the dementia stage (Dubois *et al.*, 2010; Albert *et al.*, 2011). Symptoms of the so-called “prodromal AD” (or MCI due to AD) usually consist of amnesic MCI. Prodromal AD characterizes clinically affected patients who do not yet have dementia (predementia) and who are diagnosed to have AD on the basis of their clinical presentation and supportive evidence of Alzheimer’s pathology from biomarkers.

However, prodromal AD is neither limited to nor the only cause of amnesic MCI (Gauthier *et al.*, 2006). Amnesic MCI may be caused by other neurodegenerative diseases or vascular lesions. As the use of powerful AD biomarkers (A β and neuronal injury biomarkers) has extended the spectrum of the prodromal manifestations of AD, there is a need to better characterize the clinical manifestations of prodromal AD.

In this context, we took advantage of the AD Neuroimaging Initiative (ADNI) cohort to determine the specific ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) pattern of apathy without concomitant depression in MCI. Our working hypothesis was that apathy would be associated with an AD pattern of hypometabolism if it belonged to the spectrum of prodromal AD symptoms. Conversely, a metabolic pattern of its own would prompt to consider apathy as a comorbid or premorbid neuropsychiatric feature (presence of apathy as additional disorders co-occurring with AD).

Material and methods

Setting

The ADNI is a longitudinal multisite (57 sites) observational study of healthy older subjects, MCI, and AD

subjects. MRI 1.5T, urine serum, and cerebrospinal fluid biomarkers as well as clinical/psychometric assessments are acquired at multiple time points (visits every 6 months for all the participants). Some subjects have also MRI 3T (25%), FDG-PET (50%), ¹¹C Pittsburgh compound PIB-PET. For additional information about ADNI, see www.adni-info.org. Demographic information and clinical data utilized for this study were downloaded from the ADNI clinical data repository (https://www.loni.ucla.edu/ADNI/Data/ADCS_Download.jsp). The 25 April 2011 version of the ADNI 1 clinical database was used for all analyses.

Participants

Participants who met the criteria for MCI at baseline constituted the sample for the ADNI cohort. The criteria for diagnosis of MCI included the following: (i) age between 55 and 90 years; (ii) complaints of memory loss by the patient and confirmed by a family relative; (iii) Mini mental state examination (MMSE) (Folstein *et al.*, 1975) score of 24 and higher; (iv) overall Clinical Dementia Rating Scale (Morris, 1993) score of 0.5; and (v) quantitative evidence of memory impairment relative to age and education-matched peers. Exclusion criteria at baseline included the following: (i) the presence of major depressive disorder or significant symptoms of depression (Geriatric Depression screening Scale [GDS] score of 6 or higher (Yesavage *et al.*, 1982)); (ii) modified Hachinski ischemia score greater than 5; (iii) significant neurological or psychiatric illness; (iv) use of antidepressant drugs with anticholinergic side effects; and (v) high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication, and use of narcotic analgesics.

Diagnoses of dementia were made by consensus panel of experts on the basis of the National Institute of Neurological and Communicative Disorders and Stroke/AD and Related Disorders Association criteria (McKhann *et al.*, 1984). All subjects and/or authorized representatives gave written informed consent to participate in this study, which was approved by the responsible ethics committee.

From this ADNI cohort, we systematically selected all MCI patients who underwent an FDG-PET scan and whose neuropsychiatric inventory questionnaire (NPI-Q) (Kaufer *et al.*, 2000) data were available (Figure 1).

Cognitive and psychiatric measures

Cognitive functions were assessed using the MMSE, the AD Assessment Scale-Cognitive subscale (Rosen

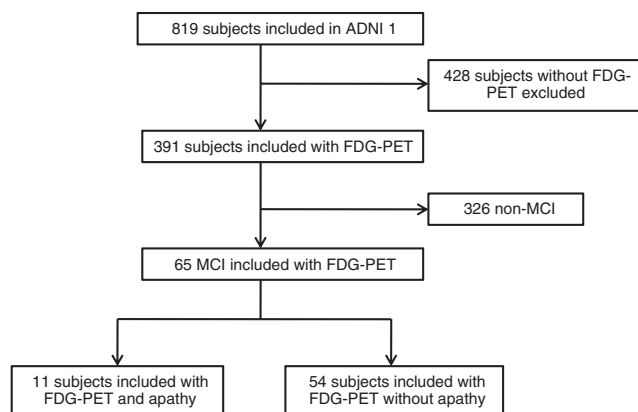


Figure 1 Flow chart of the study.

et al., 1984), category fluency test, Trail Making Test (TMT) A and B. Behavioral and neuropsychiatric impairment was examined with the NPI-Q (Kaufer *et al.*, 2000). Depressive symptoms were examined with the 15-items Global Depression Scale (Burke *et al.*, 1991). At baseline, patients were categorized as apathetic when NPI-Q apathy score was ≥ 1 .

MRI measures

All subjects have 1.5-T structural MRI. Baseline MRI scans with evidence of infection, infarction, or other focal lesions, subjects with multiple lacunes or lacunes in a critical memory structure are excluded. Acquisition of 1.5-T MRI data at each performance site followed a standardized protocol that was rigorously validated across sites. The protocol included a high-resolution, T1-weighted sagittal volumetric magnetization prepared rapid gradient echo sequence and axial proton density/T2-weighted fast spin echo sequence. The ADNI MRI core optimized the acquisition parameters of these sequences for each make and model of scanner included in the study. All vetted raw scan data were transferred to the University of California, Davis, Imaging of Dementia and Aging Laboratory for analysis.

During the first 2 years of this project, the MRI scans obtained at baseline have been analyzed by different investigators, with different methods. All results have been uploaded to the Laboratory of Neuro Imaging (LONI) and available to all investigators and the public. We have downloaded from LONI MRI analysis results of the following: (i) whole-brain segmentation using an automated version of the MGH Center for Morphometric Analysis method to produce a complete voxel-based segmentation/parcelation of the

brain performed by Anders Dale Lab (UCSD) (Fischl *et al.*, 2002) and (ii) cerebrovascular disease quantitative assessment (hyperintensity volume) performed by Charles DeCarli (Atwood *et al.*, 2004).

PET imaging

Baseline FDG-PET data were obtained from the ADNI. All ADNI subjects underwent PET scanning procedures between January 2005 and December 2007 to study cerebral glucose metabolism. In total, 65 subjects were injected with a dose of ^{18}F -FDG in a resting state in a quiet darkened room. All sites performed 3D data acquisition, provided images corrected for Compton scatter, and measured attenuation correction based upon “transmission” and “blank” scans for those systems having rod sources or by CT scan for those sites having a PET/CT scanner. Raw PET data were finally converted to DICOM (NEMA, Arlington, Virginia, USA) file format.

Statistical analysis

Baseline differences between subgroup with apathy (apathy+) and subgroup without apathy (apathy-) subjects were analyzed using *t*-tests for continuous variables and χ^2 tests for categorical variables.

The FDG-PET data were analyzed, in blind, using Statistical Parametric Mapping 8 (SPM, Wellcome department, London, England). The data sets were transformed to a standard 3D space as defined by Montreal Neurological Institute (FDG template in SPM 8 version), normalized and smoothed with an isotropic Gaussian Kernel of full width at half maximum of 8 mm (to limit PET scanner effect). Proportional scaling was used for global normalization. The SPM *t*-values of every subject were compared with the threshold using a $p < 0.001$. We retained as significant those clusters with a spatial extent $k > 100$ voxels.

Results

Study population and neuropsychiatric assessment

Sixty-five MCI participants from the ADNI study were selected. In this cohort, 11 patients were apathetic, and 54 were apathy-free. The two subgroups did not differ in age, gender, education, and ApoE genotype (Table 1).

Cognitive function assessed by MMSE and AD Assessment Scale-Cognitive subscale, Category fluency test and TMT-A did not differ between apathetic and non-apathetic patients (Table 1). TMT-B score seems

Table 1 Characteristics of study population at baseline

	Whole population	Apathy–	Apathy+	<i>p</i> -value*
Number	65	54	11	–
Subject demographics				
Age (mean ± SD)	74.8 ± 7	74.2 ± 7.4	77.6 ± 1.3	0.074
Gender (number male/female)	48/17	40/14	8/3	0.926
Years of education (mean ± SD)	15.6 ± 2.6	15.6 ± 2.5	15.5 ± 3.2	0.907
Psychotropic drug number (mean ± SD)	0.2 ± 0.4	0.1 ± 0.1	0.3 ± 0.1	0.132
Cholinesterase inhibitors (%)	35.4	39.6	16.6	0.133
Memantine (%)	12.3	13.2	8.3	0.643
APOE ε4 gene dose				
No copies (%)	50.8	51.9	45.5	0.917
One copy (%)	40	38.8	45.5	–
Two copies (%)	9.2	9.3	9	–
Cognitive scores				
MMSE score (mean ± SD)	27.5 ± 1.7	27.6 ± 1.7	26.8 ± 1.6	0.932
ADAS-Cog score (mean ± SD)	10.7 ± 4.4	10.6 ± 4.3	11.3 ± 4.8	0.315
Trail Making Test A, time in seconds (mean ± SD)	40.6 ± 22.1	41.9 ± 3.4	35 ± 3.4	0.353
Trail Making Test B, time in seconds (mean ± SD)	122.6 ± 60.6	114.7 ± 8.1	157.1 ± 20.8	0.035
Category Fluency Test, number of animals named (mean ± SD)	16.2 ± 5	16.1 ± 0.7	16.4 ± 1.5	0.837
Category Fluency Test, number of vegetables named (mean ± SD)	11.1 ± 3.4	11.2 ± 0.5	10.6 ± 1.1	1.091
Behavioral scores				
NPI-Q apathy score (mean ± SD)	0.2 ± 0.5	0 ± 0	1.2 ± 0.1	<0.001
NPI-Q total score (mean ± SD)	1.7 ± 2.5	1.5 ± 2.6	2.9 ± 1.8	0.041
NPI-Q total score without NPI apathy score (mean ± SD)	1.5 ± 2.5	1.5 ± 2.6	1.7 ± 1.7	0.626
GDS score (mean ± SD)	1.6 ± 1.4	1.4 ± 1.3	2.5 ± 1.8	0.009
GDS score without items 2, 9 and 13 (mean ± SD)	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.3	0.548
MRI analysis				
Whole brain volume, mm ³ (mean ± SD)	421,405.7 ± 467,777.8	378,838.6 ± 64,590.4	605,863.3 ± 129,654.4	0.131
Ventricles volume, mm ³ (mean ± SD)	49,122.8 ± 25,645.4	44,239.6 ± 2825.1	49,122.8 ± 3205.7	0.001
Left hippocampus volume, mm ³ (mean ± SD)	3244.7 ± 569.4	3280.9 ± 77.6	3087.6 ± 175.7	0.293
Right hippocampus volume, mm ³ (mean ± SD)	3427.6 ± 554.8	3455.6 ± 78	3306.7 ± 151.8	0.406
WMH volume, cm ³ (mean ± SD)	0.8 ± 3.5	0.9 ± 0.5	0.5 ± 0.1	0.678

Apathy–, subgroup without apathy; apathy+, subgroup with apathy; MMSE, Mini mental state examination; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; NPI-Q, Neuropsychiatric Inventory Questionnaire; GDS, Geriatric Depression Scale.

**p*-values correspond to the comparison between apathy+ and apathy– subgroups.

significantly different between apathetic and non-apatetic patients. Comparison between neuropsychiatric measures revealed that apathetic patients had a significantly higher NPI-Q score than non-apatetic patients ($p = 0.041$). The difference did not remain significant when removing the apathy item ($p = 0.626$). Apathetic patients had also a higher GDS score than non-apatetic patients ($p = 0.009$). The difference did not remain significant when removing items 2, 9, and 13 (loss of initiative, psychomotor slowing, and lack of energy), which are apathy-related ($p = 0.548$) (Table 1).

MRI results

Cerebral atrophy assessed by whole brain volume, left hippocampus volume, and right hippocampus

volume (selected for the MRI volumetric analysis as a robust neuronal injury biomarker) did not differ between apathetic and non-apatetic patients with the exception of ventricular volumes in apathetic group, which is a marker of global cerebral atrophy (Table 1). Cerebrovascular disease assessed by white matter hyperintensities volume did not differ between apathetic and non-apatetic patients (Table 1).

Brain metabolism

Group comparison, between apathetic and non-apatetic subjects, with our SPM analysis (Figure 1 and Table 2) revealed a significant decrease of glucose cerebral metabolism over the posterior cingulum for subjects with apathy (Figure 2 and Table 2).

Table 2 Results of statistical parametric mapping analysis

Anatomical region	Coordinates			<i>p</i> -value	
	<i>x</i>	<i>y</i>	<i>z</i>	Uncorrected	Z score
Left cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	-10	-36	40	<0.001	4.56
Right cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	2	-26	32	<0.001	3.96
Left cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	14	-34	42	<0.001	3.93

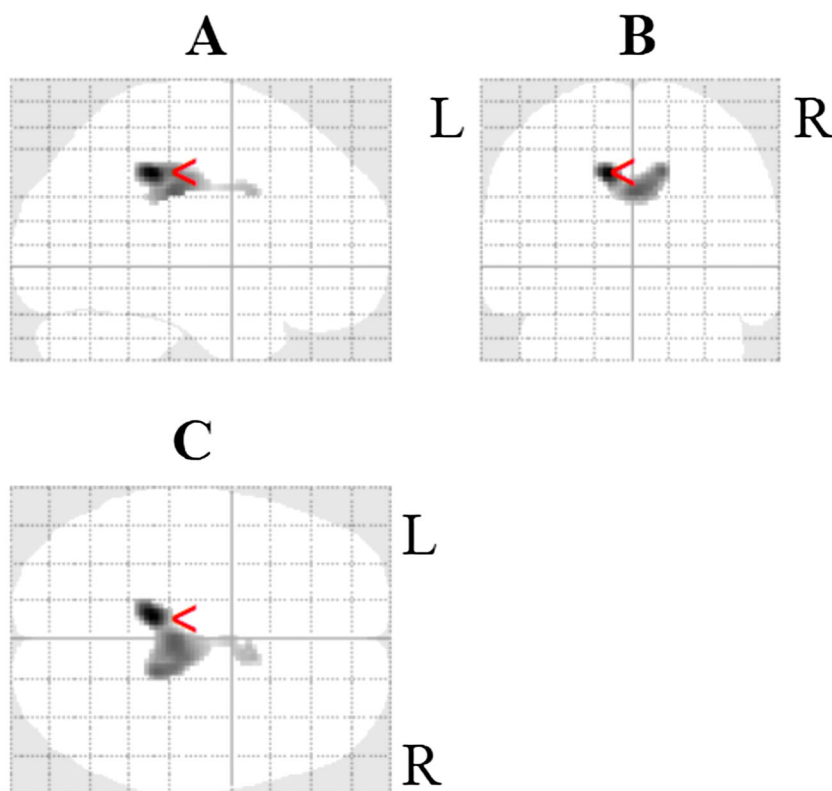


Figure 2 Statistical parametric mapping eight projections showing corrected areas with reduced glucose cerebral metabolism in MCI subjects apathy+ compared with MCI subjects apathy-.

Discussion

The main outcome of the present study is the identification of an apathy-associated glucose hypometabolism in the posterior cingulate that matches the pattern of prodromal AD.

Our study is the first to investigate specifically the metabolic pattern of apathy in MCI using FDG-PET. Functional neuroimaging studies have consistently implicated a hypometabolism in the anterior cingulate and frontal cortex as being the neuroanatomical correlate of apathy in AD (Benoit *et al.*, 2002; Benoit *et al.*, 2004; Holthoff *et al.*, 2005; Marshall *et al.*, 2007). Most studies however were performed in demented patients comparing a subgroup with apathy to a subgroup

without apathy. So far, none have sought to investigate the specific pattern of apathy in MCI subjects. In a small SPECT study of 13 cognitively impaired non-demented subjects, Migneco *et al.* showed that anterior cingulate hypoperfusion still differentiated apathetic from non-apatetic subjects (Migneco *et al.*, 2001). However, beyond the limited size of the sample, the subgroup of non-demented subjects was heterogeneous, nine of them corresponding to the current definition of MCI and four to psychiatric conditions. In the present work, we used a perfectly defined MCI population (core clinical criteria with A β biomarkers untested) in which confounding factors such as clinically significant differences in cognition (Benoit *et al.*, 2008) or cerebrovascular disease burden (Jonsson *et al.*, 2010)

were systematically ruled out. Our finding that apathetic traits were associated with a posterior cingulate glucose hypometabolism in MCI is thus genuine.

Considering that apathetic symptoms are a major risk factor for conversion to dementia in MCI subjects (Vicini Chilovi *et al.*, 2009; Richard *et al.*, 2012), it is hardly surprising that the metabolic pattern of apathy in MCI matches in part the one of AD. Our results are striking however by showing that the apathy-associated metabolic pattern does not extend beyond the one of prodromal AD. Indeed, the earliest metabolic deficits of AD occur in the parietal-temporal cortex and in the posterior cingulate (retrosplenial) region (Chetelat *et al.*, 2003; Drzezga *et al.*, 2003; Nestor *et al.*, 2003; Mosconi *et al.*, 2004), the latter showing the greatest metabolic reduction (Minoshima *et al.*, 1997). Moreover, early metabolic reductions in the posterior cingulate are thought to represent a more specific marker of AD than hippocampal hypometabolism and atrophy (Drzezga *et al.*, 2003; Nestor *et al.*, 2003). As a whole, the apathy-specific metabolic reduction in MCI closely reproduces the core metabolic deficit of prodromal AD.

Interestingly, functional neuroimaging results on depression in MCI are in sharp contrast with the ones on apathy. Lee and colleagues showed that depression in MCI is associated with lower glucose metabolism in the frontal region (Lee *et al.*, 2010), a pattern that differs from the one of prodromal AD. The latter supports the view that depression is a comorbid rather than an associated feature of prodromal AD, with a metabolic pattern of its own (Staffen *et al.*, 2009). In line with this, late-onset depression is a cause of MCI in itself (Mackin *et al.*, 2012), and consequently, depression is (if at all) a modest risk factor for conversion to dementia (Vicini Chilovi *et al.*, 2009; Palmer *et al.*, 2010). Co-occurrent apathy is probably a major confounding factor that should be considered in latter studies.

A recent ADNI study showed that for subjects with amnesic MCI who had an AD pattern of hypometabolism on FDG-PET, the risk of progression to AD during the next 2 years was 11.7 times the risk among subjects who did not have this pattern (Landau *et al.*, 2010). Therefore, the congruent metabolic patterns between apathetic amnesic MCI and early prodromal AD strongly suggest that most of the apathetic MCI patients have MCI due to AD (intermediate likelihood with biomarker of neuronal injury as FDG-PET positive and biomarker of A β deposition untested). The absence of deviation from the canonical metabolic pattern of early AD further implies that apathy belongs to the common symptoms of prodromal AD. Clinical data could support this assumption: the presence of mild signs of apathy in MCI patients has

been associated with a higher degree of memory impairment (Robert *et al.*, 2006a) and worse executive functioning (Drijgers *et al.*, 2011). Beyond AD, apathy could be considered as a common manifestation in other neurodegenerative conditions such as Parkinson's disease, dementia, and Huntington's disease, where it is related to neurodegeneration and connected to cognitive dysfunction and functional decline (Naarding *et al.*, 2009; Starkstein *et al.*, 2009). Altogether, apathy could be viewed in AD as in many neurological disorders as a direct consequence of a neurodegenerative process rather than as a comorbid psychiatric syndrome.

Obviously, the diagnosis of apathy using isolated items of the NPI scale (whose validity to diagnose apathy in MCI is unknown) was the main limitation of our study. It is unclear that a single question will provide adequate validity for this complex syndrome. Furthermore, MCI subjects with apathy in our study have very mild apathetic trait. Given that the ADNI inclusion/exclusion criteria (i.e., the GDS cut-off), it is not surprising that mostly mildly apathetic MCI subjects are included. However, TMT-B score seems significantly lower in apathy+ group in this study, which is not surprising according to relation between apathy and executive functioning. The slowing of processing, which is frequent when apathy+ patients have to deal with a dual task, could explain this result. We acknowledge that a thorough neuropsychiatric evaluation would have increased diagnostic confidence and allowed a clear distinction between apathy and depression. However, until consensus diagnostic criteria are available (Robert *et al.*, 2009), the NPI apathy item remains the most widely used instrument in clinical research on apathy. Lack of interest, which is the domain of apathy evaluated by the NPI item, is one of the core apathetic symptoms (Robert *et al.*, 2009). Additionally, concomitant depression, which is a major confounding factor in apathy diagnosis, has been ruled out in the ADNI cohort by means of the GDS scale, giving a relative confidence that recruited patients have isolated apathetic traits.

However, although not reaching the threshold for depression, the GDS score was higher in the apathy group, which raises the possibility that the difference between groups is attributable to subclinical depression. Yet as has been shown earlier, there is an apathy dimension in the GDS (Adams, 2001) (Mortby ME *et al.*, *Aging Clin Exp Res* 2012, 24: 305–16). Indeed, both depression and apathy are characterized by the loss of initiative, psychomotor slowing, and lack of energy described in items 2, 9, and 13, respectively (Adams, 2001). Accordingly, the difference between apathetic and non-apathetic subjects fails to reach significance when these items are withdrawn from the GDS.

The heterogeneous nature of MCI is another limitation of the study. Indeed, AD is not the only cause of MCI (Gauthier *et al.*, 2006). Apathy being an acknowledged risk factor for AD, we anticipated that the metabolic deficits specific for AD would scramble the signal. Therefore, our study did not aim at identifying the neural bases of apathy in MCI. Further studies on apathy will have to dissociate MCI due to AD or prodromal AD from other causes of MCI in a bigger and better defined cohort in order to check whether anterior cingulate dysfunction can still be considered as the neuroanatomical correlate of apathy in prodromal AD, as it is in AD. Hopefully, future cohorts such as ADNI 2 will provide sufficient data to investigate this. Furthermore, the degree of apathy in the ADNI cohort is quite low, with likely about two-thirds of the subjects having no more than mild symptoms as measured by the NPI-Q. One interpretation of the current results is that the mild degree of apathy seen in the cohort is insufficient for the detection of anterior cingulate hypometabolism but is still associated with a greater likelihood of underlying AD pathology (as measured by greater posterior cingulate hypometabolism).

Altogether, neuroimaging data from the first ADNI cohort strongly suggest that apathy is a prodrome rather than a risk factor of AD.

Conflict of interest

None declared.

Key points

- There was no difference between apathy and apathy-free mild cognitive impairment (MCI) patients regarding cognitive assessment and neuropsychiatric measures when apathy-specific items were removed.
- Cerebrovascular disease load and cerebral atrophy were equivalent in both groups.
- Compared with the apathy-free MCI patients, MCI patients with apathy had significantly decreased metabolism in the posterior cingulate cortex (Alzheimer's disease-specific pattern of brain metabolic defect).
- These results could suggest that apathy belongs to the spectrum of prodromal Alzheimer's disease symptoms.

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