Apathy in corticobasal degeneration: possible parietal involvement

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Summary

Corticobasal degeneration is a rare disorder, which usually consists of a combination of complex movement disorders, apraxia and cortical changes. Its definition is still evolving and in 2013 an international consortium tried to develop new criteria, based on a systematic literature review. Over a long period of time, we carefully selected 23 patients who fulfilled the criteria for a diagnosis of corticobasal degeneration; all had the so-called corticobasal syndrome phenotype, in accordance with Armstrong et al. (2013). Through a dedicated study, we set out to study behavioral alterations, specifically apathy, and to compare the results obtained with those deriving from a well-defined Parkinson's disease population.
On the basis of our limited but specific results, we argue for a possible role of the parietal neural networks as a determinant of apathy, and provide an overview of emerging data in the imaging and pathology literature.

KEY WORDS: apathy, clinician-rated corticobasal degeneration (cr-CBD), corticobasal syndrome (CBS), parietal network.

Introduction

Corticobasal degeneration (CBD) is recognized as an asymmetric, neurodegenerative disorder associated with pathological accumulation of tau protein. It causes disruption of body motor schemata and significant impairment of higher cortical functions, and is characterized by a combination of cortical and basal ganglia signs (Togasaki et al., 2000). Its most distinctive clinical feature is its unilateral, or markedly asymmetric, presentation; indeed, among the entire constellation of parkinsonian syndromes, only idiopathic Parkinson's disease (PD) has been found to present, at the earliest stage, such an asymmetry (Reich et al., 2009; Armstrong et al., 2013).
Different presentation phenotypes have been associated with this pathology: probable/possible corticobasal syndrome (CBS), frontal behavioral spatial syndrome, the non-fluent/agrammatic variant of primary progressive aphasia, and progressive supranuclear palsy syndrome (Armstrong et al., 2013). To facilitate diagnosis in neurological settings, the current diagnostic criteria have been categorized, on the basis of the different presentation phenotypes, into two different sets to allow two different diagnoses.
The first set is more reliable for clinical and research purposes and, accordingly, results in a diagnosis termed cr-CBD; this diagnosis requires a presentation pattern that mainly includes the motor feature as described in the probable CBS phenotype and only a few higher cortical features such as the alien limb phenomenon, limb apraxia, some behavioral changes or general aspecific cognitive impairment (Armstrong et al., 2013).
The second set is less specific, and allows a diagnosis of possible corticobasal degeneration (p-CBD) (Togasaki et al., 2000); this diagnosis requires the presence of the possible CBS phenotype, but otherwise the criteria are less restrictive, including a positive family history and possibly a genetically defined mutation of tau protein; there is no minimum age at onset (Armstrong et al., 2013).
Clinical diagnosis of CBD is challenging for three reasons: the full complement of findings is rarely found at presentation; moreover, if CBD is not clinically suspected, subtle but relevant findings (e.g. extinction, language impairment, myoclonus or apraxia) may not be searched for, or may not be properly appreciated; the clinical picture of CBD has some substantial overlaps with a huge variety of other parkinsonian and dementing illnesses (Reich and Grill, 2009).
Behavioral aspects of CBD have been described, but not fully studied, in specific series.
In the present study we set out to focus on a specific behavioral symptom, apathy, with the aim of clarifying its importance among other neuropsychological symptoms in two groups of patients: one group affected by cr-CBD and the other by idiopathic PD. PD is a simpler and more common clinical condition than cr-CBD. Apathy is an intriguing symptom in PD, too, and one of the most studied in recent years (Moretti and Signori, 2016); it has been considered one of its most disturbing psychiatric symptoms (Starkstein and Leentjens, 2008). Some studies have related PD apathy to dysfunction of the nigro-striatal pathway (Starkstein et al., 1992; Cutberth and Insel, 2013; Stuss et al., 2000), a suggestion supported by functional connectivity studies (Rejinders et al., 2010; Robert et al., 2012) and evidence of a marked impairment of connectivity in striatal and ventrolateral prefrontal regions (Baggio et al., 2015), although data remain controversial (Huang et al., 2013; Skidmore et al., 2013; Kos et al., 2016; Moretti and Signori, 2016).
In the present paper, we examine our findings and discuss the emerging role of parietal-frontal loops as one of the most recently discovered neural correlates underlying apathy in motor-dominant pathologies.

Materials and methods

Over a period of time (1st January 2005 to 1st July 2014) that was necessarily long due to the low prevalence rate of CBD, we collected data relating to 23 patients (12 males and 11 females) who came to our observation and were given a diagnosis of cr-CBD. These patients were included in study Group A. A comparison group, Group B, comprised 96 patients with PD, all of whom met the criteria for a diagnosis of idiopathic PD (Hughes et al., 1992).

Magnetic resonance imaging (MRI) was performed in all the patients in both the groups at baseline; the baseline characteristics are reported in Table I.

The patients in Group A had a mean age of 63.5 ± 2.4 years, all of them were right-handed (with a mean score of +22.6 on the Briggs and Nebes test) (Briggs and Nebes, 1975). When recruited, all these patients showed an asymmetric akinetic syndrome, associated with bradykinesia, alien limb syndrome, gait difficulties and slurred speech, which had developed over an average period of 9.6 ± 6.3 months prior to the diagnosis. No patient reported specific cognitive impairment. Objectively, none of the 23 patients responded to levodopa therapy. Parkinsonism is associated with characteristic dystonic postures of the arm and hand (flexed and adducted arm) and the baseline neurological evaluation of the Group A patients showed:

- focal and stimulus-sensitive myoclonus in 4 patients;
- asymmetric ideomotor apraxia in 19 patients;
- alien hand syndrome in 3 patients;
- astereognosia in 7 patients, 2 of whom showed visual neglect;
- a defect of up-gaze movements in 16 patients;
- speech disruption, characterized by low vocal intensity, mono-loudness, and slurred articulation, in 7 patients.

All these patients, both at the time of recruitment (baseline) and at the end of the one-year follow-up, underwent a brain MRI scan, performed with a 1.5T magnet. The examination was performed using axial and coronal slices, employing the following sequences: T1, SE proton density and T2-weighted sequences (TR/TE: 2780/2080), turbo-FLAIR (TR/TE/TI: 9832/150/2000) and TSE T2-weighted sequences (TR/TE: 2876/120). The results at baseline were the following:

- 18 patients presented asymmetrical parietal cortical atrophy contralateral to the more affected limbs;
- 8 patients showed both asymmetrical frontal and parietal atrophy, mostly involving the posterior frontal areas on the side contralateral to the clinically more affected one;
- 5 patients displayed bilateral parietal atrophy;
- 7 patients showed evident enlargement of the lateral ventricle on the same side as the more affected parietal area, with subcortical atrophy of the white matter bulk of the corresponding parietal area. The fronto-parietal distribution of the atrophy was best appreciated on sagittal T1-weighted images;
- 13 patients showed a loss of the putamen signal on high-field T2-weighted MRI.

The results at one year of follow-up may be summarized as follows:

- 23 patients showed asymmetrical parietal cortical atrophy contralateral to the more affected limbs;
- 12 showed asymmetrical frontal and parietal atrophy in the hemisphere contralateral to the clinically more affected side;
- 10 patients displayed bilateral parietal atrophy;
- 15 patients showed subcortical atrophy of the white matter bulk of the corresponding parietal area.
- 17 patients showed a loss of the putamen signal on high-field T2-weighted MRI.

The comparison group, Group B, was recruited by enrolling 96 consecutive outpatients with PD who met the criteria for a diagnosis of idiopathic PD (Hughes et al., 1992). They had a mean age of 58.1 ± 4.1 years, and a mean age at disease onset of 54.7 ± 3.1 years. Their mean disease duration was 3.3 ± 1.5 years. At their baseline evaluation, all these patients underwent brain MRI with a 1.5 T magnet; this examination was repeated at the one-year follow-up. In accordance with the criteria for a diagnosis of idiopathic PD (Hughes et al., 1992), we did not find any specific alteration of brain images at baseline or one year later. Patients were evaluated in ON-pharmacological states. The mean L-dopa equivalent dosage was 660 ± 130.5 mg/day. Forty-two patients received dopamine agonists during their treatment.

All the patients were followed for a period of 12 months starting from their recruitment date through periodic neurological and neuropsychological examinations. Follow-up visits were scheduled to take place at 1, 4, 8, and 12 months from baseline. A complete neuropsychological examination was conducted at baseline and at the last visit, and the results were compared.

The trial was performed in accordance with the Declaration of Helsinki and with our institute's ethical guidelines. Written informed consent was obtained from all the participants prior to the study.

Outcomes measures

The main outcomes of the study are described below.

1. Global performance was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005); MoCA results are reported as raw scores, and as scores adjusted for age and education, expressed as years of schooling (Conti et al., 2015; Santangelo et al., 2015).
2. Executive functions, attention, judgment and analogical reasoning were assessed using the Frontal Assessment Battery (FAB) (Dubois et al., 2000).
3. Raven's Standard Progressive Matrices were employed to assess logical judgment and analogical resolution of problems (Raven et al., 1981).
4. Apathy was assessed using the clinician-/researcher-rated version of the Apathy Evaluation Scale (AES-C), and the parallel self-report version of the same instrument (AES-S) (Marin et al., 1991).
5. Global behavioral symptoms were assessed using the Neuro-Psychiatric Inventory, NPI (Cummings et al., 1994); symptom frequency was rated on a scale of 1 to 4 (1 = less than once a week; 2 = once a week; 3 = several times a week; 4 = every day), and severity was rated on a scale of 1 to 3 (1 = mild; 2 = moderate; 3 = severe). A composite score ranging from 1 to 12, defined as the product of frequency and severity, was calculated. Caregiver distress was also recorded and scored for each neuropsy-

Table I - Comparison of mean values of age, gender, handedness and educational level in patients with corticobasal degeneration (Group A) and Parkinson's disease (Group B).

Characteristics	Group A	Group B	F chi2 value	DF	p-value
Age	63.5 (2.4)	58.1 (4.1)	2.76	2.24	0.09
Gender (male/female)	12/11	49/47	0.81	2	0.75
Handedness	22.6 (1.2)	22.1 (1.4)	0.79	2	0.83
Educational level (years)	7.7 (3.4)	8.1 (2.4)	0.67	3.1	0.45
Response to DOPA	0	+	NA	NA	NA

Abbreviations: DF= degree freedom; NA= not applicable. Values are expressed as mean (SD).

Table II - Cognitive parameters at baseline and at 12 months. MOCA scores have been reported corrected for Italian normative values –in the text. Values are mean (SD).

	Baseline Group A	Baseline Group B	12 months Group A within-group (12 months vs baseline) p-value	12 months Group B within-group (12 months vs baseline) p-value	12 months Between-groups (B vs A) p-value
MOCA	27.1 (0.9)	28.1 (0.3)	25.3 (0.2) p<0.05	27.3 (0.4)	+2.0 (0.2)
RAVEN'S STANDARD MATRICES	123.8 (5.6)	134.1 (2.3)	119.1 (4.5)	123.1 (6.7)	+4 (2.2)
FAB total score (0-18)	12.2 (0.5)	14.2 (0.5)	10.1 (1.1)*	13.6 (0.3)	+3.5 (0.8)**
Analogies	2.5 (0.2)	2.6 (0.3)	1.9 (0.6)*	2.2 (0.3)	+0.3 (04)*
Phonemic fluency	2.4 (0.2)	2.7 (0.3)	1.3 (0.5)*	2.1 (0.2)	+0.8 (0.2)*
Motor series	2.1 (0.7)	2.3 (0.1)	1.6 (0.2)*	1.9 (0.2)	+0.3 (0.2)
Contrast instructions	2.1 (0.8)	2.5 (0.3)	1.6 (0.5)*	2.6 (0.7)	+1.0 (0.2)*
Go/no-go	1.6 (0.5)	2.1 (0.5)	0.7 (0.4)*	2.1 (0.6)	+1.4 (0.2)*
Prehension behavior	1.5 (0.9)	1.9 (0.9)	0.5 (0.8)*	1.5 (0.3)	+1.0 (0.5)*

Abbreviations: MOCA= Montreal Cognitive Assessment; FAB= Frontal Assessment Battery.
MOCA scores are reported corrected for Italian normative values (see text). Values are expressed as mean (SD).
* p<0.05; **p<0.01

chiatric symptom complex. The caregiver was asked to rate their own emotional or psychological distress caused by each symptom on a scale of 0 to 5 (0 = no distress; 1 = minimal; 2 = mild; 3 = moderate; 4 = moderately severe; 5 = very severe distress). A total caregiver distress score was obtained by summing the individual scores on the 12 items.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0). Within-group changes from baseline to 12 months were tested using the Wilcoxon Signed Ranks test. Between-group comparisons of changes from baseline were tested using the Wilcoxon two-sample test.
This was done for the overall scores for each efficacy variable. In addition, sub-analyses of behavioral data obtained at baseline and at 12 months using the AES and NPI were performed to determine which items of these scales showed particular deterioration. Results are presented as mean changes from baseline with standard deviations, and p-values are presented where appropriate.

Results

Baseline demographic variables are reported in Table I. The demographic variables age, gender, handedness and years of education were not significantly associated with either of the two clinical conditions.

Table II, showing numerical data, provides a synopsis of the cognitive performances in the two groups. At baseline, all the patients performed quite well on the MoCA and Raven's Standard Progressive Matrices, used to evaluate general cognition, and the FAB, analyzing frontal executive and abstract reasoning (considering both the total score and the specific sub-items). We did not find any significant within-group differences in either of the two groups at baseline, according to a Wilcoxon Signed Rank Test. At the 12-month follow-up, within-group comparisons (Wilcoxon Signed Rank test) showed that the group A patients showed worse than baseline performances on the MoCA (-1.8 (0.7), $p<0.05$) and on FAB, both for the global score [-2.1 (0.6), $p<0.05$], and all the sub-scores: analogies [-0.6 (0.2), $p<0.05$], phonemic fluency [-1.1 (0.7), $p<0.05$], motor series [-0.5 (0.2), $p<0.05$], contrast instructions [-0.5 (0.7), $p<0.05$], go/no-go instructions [-0.9 (0.2), $p<0.05$], prehension behavior [-1.0 (0.1), $p<0.05$]; the results remained within the range of normal values. On the other hand, no differences emerged at 12 months compared to baseline in Group B.

The between-groups differences recorded at 12 months, evaluated using the Wilcoxon Two Sample Test, are also reported in Table II. With the exception of the motor series sub-item of FAB and the Raven's Standard Progressive Matrices scores, all the item scores differed significantly between the groups.

At the end of the 12-month study, no subject in Group A was able to mime to verbal commands given by the examiner, while they were slightly better able to imitate the examiner performing mimes: they showed signs of ideomotor apraxia, not ideational apraxia, of the affected hand. On the contrary, when given a specific tool, their performance with the affected hand was virtually normal, although the movements were awkward and slightly clumsy. With the opposite hand they were able to carry out orders properly and could mime quite well. These patients recognized only the less affected personal and extrapersonal hemispace, and they showed modest signs of bucco-facial apraxia.

Table III reports the baseline NPI results, giving the sub-item scores; the incidence of symptoms in both groups was described through a comparison between groups (t-test).

From a behavioral perspective, CBD is more complex than PD. From the start of the study, the Group A (CBD) patients displayed more agitation and aggression, depression, anxiety and appetite changes than the Group B (PD) patients ($p<0.01$); on the other hand, Group B showed more irritability than Group A ($p<0.01$). Apathy was found in 87% of the Group A patients, but in only 24% of the PD patients at recruitment ($p<0.01$).

Composite scores (ranging from 1 to 12), defined as the product of frequency and severity, were calculated for each NPI item in each group. The most salient findings were the higher scores for depression and apathy recorded in Group A compared with Group B ($p<0.01$). We estimated and recorded caregiver distress, too: in both groups, caregivers reported increased distress due to apathy and sleep changes.

Table IV presents the NPI results at the 12-month evaluation, giving the incidence of symptoms in both groups; it also reports comparisons both within groups (12 months *vs* baseline) and between groups (at 12 months). The former showed a higher incidence of agitation, depression, irritability, apathy, appetite and sleep behavior changes ($p<0.01$) at 12 months *versus* baseline in Group A, and increased agitation, apathy and appetite changes ($p<0.01$) in Group B. With regard to the between-groups comparison, a Wilcoxon two-sample test showed a significant difference in Group A *vs* Group B in agitation, depression, anxiety, irritability, apathy, sleep behavior changes, disinhibition and appetite disorders (Table IV). Apathy was reported in all the Group A patients (100%), *versus* only 28% of the Group B patients. The composite scores (frequency x severity) were significantly modified at 12 months *vs* baseline (within groups) being found to be increased for agitation, depression and apathy in Group A ($p<0.01$), and for depression and disinhibition ($p<0.05$) in Group B. The groups were found to differ significantly in caregiver distress (according to a between-groups comparison, mediated by Wilcoxon two-sample test) due to agitation, depression and apathy ($p<0.05$); this distress was more evident in caregivers of Group A than of Group B patients.

While aware of the fact that neurodegenerative disorders are frequently characterized by coexistence of various behavioral problems, we recorded separately the data for the patients reporting single behavioral disturbances and for those with coexistent behavior disorders. The numbers and percentages of patients in the two groups (isolated or coexistent behavioral symptoms) are reported in Table V. The qualitative assessment of apathy (AES-S and AES-C) reflected the NPI scores, as shown in Table VI.

With regard to a possible/hypothesized correlation between regional differences on MRI and behavior reports, our study produced some interesting findings. As we did not use voxel-based morphometry or any other procedure to measure the brain volumes, we can only report a numerical correlation of behavioral symptoms with prevalent regional atrophy in CBD patients. Therefore, considering apathy as a unique symptom and also considering the coexistence of different behavioral problems, we advance some observations regarding their relationship with MRI findings.

To weigh up the qualitative apathy scores (AES-C scores), we arbitrarily applied a cut-off between scores of 30-45 and 45-60. At baseline in CBD, we found 14 patients with a score between 30 and 45: 6 of these patients showed asymmetrical parietal cortical atrophy contralateral to the more affected limbs; 3 patients showed asymmetrical posterior frontal atrophy, associated with the parietal atrophy; 2 patients showed bilateral parietal atrophy; 3 patients showed, on the more atrophic side, an evident enlargement of the lateral ventricle, associated with subcortical atrophy of the white matter bulk of the corresponding parietal area. At baseline, 6 patients had an AES-C score of between 45 and 60; 3 of these patients showed asymmetrical parietal cortical atrophy contralateral to the more affected limbs; 1 patient showed frontal and parietal atrophy, in the

Table III - Baseline NPI results in both groups: differences calculated by t-test.

NPI sub-items	Number of patients Group A (and %)	Number of patients Group B (and %)	Frequency x severity Group A	Frequency x severity Group B	Caregiver distress Group A	Caregiver distress Group B
Hallucinations	0	0	0	0	0	0
Delusions	0	0	0	0	0	0
Agitation/aggression	3 (13%)	4 (4%) **	2	2	1	1
Dysphoria/depression	13 (56%)	34 (35%) **	4 *	2	2	2
Anxiety	15 (65%)	41 (43%) **	6	6	2	2
Irritability	1 (4%)	12 (12%) **	2	2	2	2
Disinhibition	1 (4%)	4 (4%)	2	2	2	2
Euphoria	0	1 (1%)	0	2	2	2
Apathy	20 (87%)	23 (24%) **	8 **	8	4	4
Aberrant motor behavior	1 (4%)	2 (2%)	2	2	2	2
Sleep behavior change	2 (8%)	7 (7%)	4	4	3	3
Appetite change	2 (8%)	2 (2%) **	2	2	2	2

*p<0.05; **p<0.01

hemisphere contralateral to the clinically more affected side; 2 patients showed cortical parietal plus subcortical atrophy of the white matter bulk of the corresponding parietal area.

One year later, the results can be summarized as follows: 18 patients had an AES-C score of between 30 and 45 and 6 patients an AES-C score of between 45 and 60.

In the first group, 8 patients showed asymmetrical parietal cortical atrophy contralateral to the more affected limbs; 6 patients showed asymmetrical frontal and parietal atrophy; 2 patients showed, on the more atrophic side, evident subcortical atrophy of the white matter bulk of the corresponding parietal area; 2 patients showed marked bi-parietal atrophy.

In the second group, 2 patients showed asymmetrical parietal cortical atrophy contralateral to the more affected limbs; 1 patient showed both posterior frontal and parietal atrophy; 2 patients showed, on the more atrophic side, subcortical atrophy of the white matter bulk of the corresponding parietal area; 1 patient showed marked bi-parietal atrophy.

When we considered the main behavioral aspects in CBD, as shown in Table V, we found, at baseline, that 4 patients showed apathy, agitation and depression and 16 pure apathy.

The 4 with coexistent behavioral symptoms showed frontal and posterior parietal atrophy; the 16 who manifested pure apathy showed more evident parietal atrophy (isolated cortical or cortical plus subcortical atrophy). One year later, 10 patients showed a combination of apathy, agitation and depression and 19 patients isolated apathy. The former group was found to show more marked coexistence of frontal and parietal atrophy, while the latter revealed posterior parietal or bilateral parietal atrophy.

A Spearman's rank correlation analysis (at 12 months) highlighted the presence of significant correlations, in both the groups, between:

- higher NPI scores and caregiver distress ($r=0.78$, $p<0.01$);
- NPI apathy score and AES-S and AES-C ($r=0.71$, $p<0.01$ and $r=0.78$, $p<0.01$, respectively).

Discussion

Compared with specific cognitive signs of CBD, such as "limb kinesthetic apraxia" (Pillon et al., 1995), ideomotor apraxia (Massman et al., 1996), constructive apraxia (Massman et al., 1996), linguistic and speech alterations (Armstrong et al., 2013) and a dysexecutive syndrome (Pillon et al., 1995; Armstrong et al., 2013), all of which have been described and well accepted, behavioral aspects remain quite neglected in descriptions of cr-CBD (Litvan et al., 2000; Kertesz et al., 2004; Massman et al., 1996; Armstrong et al., 2013). Apathy has not been specifically studied in CBD since a key work, by Litvan et al. (1998), defined it as a salient aspect. However, since apathy is becoming increasingly recognized as very important in PD, Parkinson's disease dementia complex (PDD) and parkinsonism, new data have been drawn from neuroimaging studies in PD and PDD. In patients affected by these conditions, higher apathy and lower gray matter density values were localized in the bilateral inferior parietal gyrus and right precuneus (Reijnders et al., 2010). Skidmore et al. (2013) confirmed

these data, showing an association between apathy and altered imaging sequences in the right middle orbitofrontal cortex and bilateral subgenual cingulate cortex, the left supplementary motor cortex, the left inferior parietal lobule, and the left fusiformis gyrus (Skidmore et al., 2013); this association has also been reported in the left posterior cingulate cortex (Robert et al., 2014). Therefore, even though the frontal-subcortical regions are widely regarded as the neural correlates of apathy (Duffy et al., 2000; Kos et al., 2016), new data seem to relate apathy to parietal cortical alterations. Pathological and histochemical data confirm well-established alterations of the parietal regions in CBD (Litvan et al., 2000; Togasaki et al., 2000) and this also emerges in the new cr-CBD syndrome classification (Armstrong et al., 2013).

Against this background, our study was conducted to determine, in the context of a behavioral evaluation, the role of apathy in cr-CBD, from the time of clinical diagnosis through to the end of 12 months of follow-up, comparing the findings to those obtained in PD patients in the ON-phase. We are fully aware of the small number of patients recruited for this study, and therefore that the ideas deriving from our observations are speculative and cannot be considered axiomatic or somehow demonstrative.

Our aim, therefore, was to tentatively attribute a role to primary parietal cortical-subcortical atrophy (present in CBD patients) in defining apathy.

What we observed in our study can be summarized in the following points:

1. albeit in a limited number of patients, cr-CBD criteria were employed to allow the most specific diagnosis of this complex syndrome;
2. the cr-CBD patients showed cognitive impairments (i.e. apraxia and dysexecutive alterations) but they were not demented. On the other hand, from the very beginning, they manifested some behavior complex disorders, which progressed during the follow-up. They manifested affective disorders (depression was very frequent) and anxiety (with a remarkable incidence of somatic pain);
3. apathy is a dominant sign of behavioral impairment in cr-CBD, and it was reported as an isolated symptom in 69.5% of the cases at the beginning of the study, and in 82.6% at the end of the follow-up; among the PD patients it was reported as an isolated symptom in 20.8% at the beginning of the study and in 17.7% at the end of the follow-up;
4. cr-CBD patients with high apathy scores (or presenting apathy as an isolated symptom) showed more evident contralateral parietal cortical and subcortical atrophy; on the other hand, patients showing different behavioral symptoms associated with apathy presented posterior frontal and parietal atrophy.

Even though it is impossible to generalize, we can argue that apathy is a dominant behavior disorder in CBD, and was found to emerge quite significantly in cr-CBD. Apathy does not seem to be related to cognitive impairment but, taking into account the limits of our study (we did not use volumetric imaging measures), it was found to be related to parietal cortical/subcortical alterations. A direct measure, obtainable through a voxel-based morphometry approach for example, could provide a positive parametric demonstration of the hypothesized connections. Thus, a further limit of this study is the lack of objective measures to substantiate our speculations.

Nonetheless, we envisage that the parietal cortex will be shown to play a role in the genesis of apathy. However, data intended to establish a key role for this area must take into account its neural projections to many different brain regions, which are fundamental for motivational and attention processes. We therefore focused on certain functional neural networks that might provide an explanation of the parietal involvement in these “frontal” processes.

In fact, the inferior parietal lobule (LIP) mediates the integrative analysis of visual information, i.e. analysis of its type and spatial location (Ungerleider and Mishkin; 1982; Heilman et al., 1999). The LIP receives inputs from the cingulate gyrus, which is fundamental in orienteering attention; the LIP also collects inputs from the dorsolateral frontal lobes, related to goal-oriented behaviors (Heilman et al., 1999). Many projections from the frontal eye fields (FEFs) reach the LIP (Paus, 1996). The FEFs are involved in the preparation and triggering of intentional visually guided saccades, predictive saccades, and memory-guided saccades (Pierrot-Deseilligny et al., 2003), and in target selection and attentive polarization. The projections from the supplementary eye fields (SEFs) are directed towards the LIP (Grosbras et al., 1999); SEFs are connected with all the areas involved in eye movement control — the FEFs, the dorsolateral prefrontal cortex, the anterior cingulate cortex (Luppino et al., 2003) —, which are involved in motor visual programs, including saccadic control, peripersonal motor programs and the program for sequential saccadic movements (Pierrot-Deseilligny et al., 2003). Moreover, the posterior parietal cortex (PPC) includes the intraparietal sulcus, extending from the post-central sulcus anteriorly to the parietal-occipital sulcus posteriorly, where parietal eye fields (PEFs) appear to be located (Müri et al., 1996). PEFs are involved in the control of saccades (Leigh and Zee, 1999), but also in the visual attention process (Bilsey and Goldberg, 2003), in eye-hand coordination (Simon et al., 2002), and in the visual fixation process (Rivaud et al., 1994).

The projections from the anterior cingulate cortex and from the posterior cingulate cortex reach the PEFs (Pierrot-Deseilligny et al., 2003), and thus provide adequate control of intentional saccades (Gaymard et al., 1998).

A supposed ‘cingulate eye field’ is located at the limit between Broadmann areas 23 and 24 and it can be considered capable, via an intentional motivation process, of preparing all the frontal ocular motor areas involved in intentional saccade control to correct the forthcoming motor behavior (Goodale and Haffenden, 2003), and of controlling an eventual goal-directed action (Goodale and Haffenden, 2003).

More evidence suggests that the inferior parietal lobe (area 6) circuits have complex storage capacities, to allow memorization of elementary motor schemes and to retrieve these as required (Rizzolatti et al., 1988; Rizzolatti et al., 1988 B). Finally, it is widely accepted that many neurons of F6 become active well before movement onset (Matsuzaka et al., 1992). Most of them appear to command global reaching-grasping movements, without any indication that they are coding a specific type of grip. These data on the organization of F6 suggest that this area represents a nodal point in transmit-

Table IV - 12-month NPI results in both groups: differences calculated by t-test

NPI sub-items	Number of patients Group A within-group vs baseline t-test	Number of patients Group B within-group *vs* baseline t-test	Between groups (B vs A) t-test	Frequency x severity Group A within-group *vs* baseline t-test	Frequency x severity Group B within-group *vs* baseline t-test	Caregiver distress Group A within-group *vs* baseline t-test	Caregiver distress Group B within-group *vs* baseline t-test	Caregiver distress Between groups t-test
Hallucinations	0	0		0	0	0	0	
Delusions	0	0		0	0	0	0	
Agitation/aggression	7 (30%)	8 (8%) **	**	4	2	2	1	*
	**			*		*		
Dysphoria/depression	19 (83%)	36 (36%)	**	6	4	4	2	*
	**			*	*	*		
Anxiety	16 (66%)	42 (43%)	*	6	6	2	2	
Irritability	5 (22%)	10 (10%)	**	2	2	2	2	
	**							
Disinhibition	0	6 (6%)	**	1	4	2	2	
	**			NS	*			
Euphoria	0	2 (2%)		0	1	2	2	
Apathy	23 (100%)	27 (28%)	**	12	6	5	4	*
	**			**		*		
Aberrant motor behavior	0	2 (2%)		0	2	2	2	
	**							
Sleep behavior change	3 (13%)	7 (7%)	*	2	2	3	3	
	**							
Appetite change	5 (22%)	2 (2%)	**	2	2	2	2	
	**	**						

*p<0.05; **p<0.01

Table V - Numbers of patients in the two groups who reported different behavioral changes, isolated or in combination.

	CBD baseline (n. pts and %)	CBD 12-month follow-up (n. pts and %)	PD baseline (n. pts and %)	PD 12-month follow-up (n. pts and %)
Apathy	16 (69.5%)	19 (82.6%)	20 (20.8%)	17 (17.7%)
Apathy+agitation +depression	4 (17.3%)	12 (52.1%)	6 (6.25%)	24 (25%)
Depression+anxiety	8 (34.7%)	11 (47.8%)	12 (12.5%)	20 (20.8%)
Anxiety	10 (43.4%)	10 (43.4%)	35 (36.4%)	28 (29.1%)
Depression	10 (43.54%)	6 (26%)	27 (28%)	27 (28.7%)

Abbreviations: CBD=corticobasal degeneration; PD=Parkinson's disease

Table VI - Qualitative analysis of the Apathy Evaluation Scale results in the two groups.

	Group A Baseline	Group A 12- months (within groups Wilcoxon test)	Group B Baseline	Group B 12- months (within groups Wilcoxon test)	Between groups B *vs* A baseline/12months
AES-S	53.3 (3.2)	58.9 (1.8)	21.3 (1.5)	28.9 (1.2)	
		(+5. 6 (1.8), *)		(+7. 6 (0.4), *)	(+30. 0 (0.7), **)
AES-C	52.5 (2.1)	58.5 (1.3)	22.5 (2.7)	27.3(1.1)	
		(+6. 0(1.8), *)		(+5. 2(1.3), *)	(+31. 2 (0.7), **)

Abbreviations: AES-S=Apathy Evaluation Scale, self-report version; AES-C= Apathy Evaluation Scale, clinician-/researcher-rated version.
*p<0.05; **p<0.01

ting cognitive and motivational information from prefrontal and cingulate areas to the premotor areas.
Motivational and cognitive signals prompting movements are continuously sent to F6, where they are supplemented with information derived from posterior parietal areas (Schlaug et al., 1994).
In conclusion, the PPC compares visual information on the location of a target to be reached with an estimate of the current limb position. The most medial parts of the superior parietal lobule (including V6a, 7m, medial intraparietal) discharge and are modulated as a function of different combinations of inputs, including the direction of intended and executed arm movements, static postures, retinal input, motion of the target and visual feedback about movements of the arm, and the direction of gaze and eye movements (Kalaska et al., 2003).
All these aspects have led to the acknowledgment that the parietal lobe participates in motor and spatial control, particularly the coordinate-transformation system for sensory driven strategies of the eyes, arm and hand (Wiesendanger et al., 1997; Heilman et al., 1999). Superior parietal areas appear more involved in voluntary, anticipatory allocation of attention to peripheral locations (motor planning), whereas inferior parietal regions are activated for stimulus-driven reorienting of attention (Macaluso and Driver, 2003).
Parietal areas might contribute to the purposeful, goal-directed action, and therefore, to the complex network which guarantees visual control for planned and goal-directed actions. Parietal cortical disruption might therefore contribute to the apathy symptom in cr-CBD.

Acknowledgements

The Authors thank Joy Bates, PhD, for her valuable assistance in editing the text.

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