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Article *in* European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology · November 2010

Impact Factor: 4.37 · DOI: 10.1016/j.euroneuro.2010.07.001 · Source: PubMed

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Dopaminergic modulation of the default mode network in Parkinson's disease

Pauline Delaveau [a,b,*], Pilar Salgado-Pineda [c], Philippe Fossati [a,d,e], Tatiana Witjas [f], Jean-Philippe Azulay [f], Olivier Blin [b]

[a] *Emotion center, CNRS USR 3246, Paris, France*
[b] *CIC-UPCET and Pharmacologie Clinique, CNRS, UMR 6193 INCM, Marseille, France*
[c] *Benito Menni CASM, CIBERSAM, Barcelona, Spain*
[d] *Pierre et Marie Curie University, Paris, France*
[e] *Assistance Publique-Hôpitaux de Paris, Department of Psychiatry, Pitié-Salpêtrière Hospital, Paris, France*
[f] *Service de Neurologie et Pathologie du Mouvement, APHM, Hôpital de la Timone, Marseille, France*

Received 26 May 2010; received in revised form 30 June 2010; accepted 6 July 2010

KEYWORDS
Parkinson's disease;
Dopamine;
Brain deactivation;
fMRI;
Posterior cingulate;
Medial prefrontal cortex

Abstract

Default mode network (DMN) is characterized by a deactivation of several cortical areas (including medial prefrontal cortex and posterior cingulate cortex) during goal-directed experimental tasks. Few findings are reported on DMN and the involvement of dopaminergic medication on this network in Parkinson's disease (PD). To evaluate the effect of levodopa on DMN deactivation, we conducted a randomized, crossover, placebo-controlled experiment consisting of two fMRI assessments in fourteen non-demented, non-depressed PD patients compared to thirteen healthy volunteers. They received either acute doses of levodopa or placebo in two fMRI sessions. Brain deactivation was evaluated during a facial emotion recognition task. While the control subjects showed a classical brain deactivation pattern during the emotional task, the PD patients taking placebo only deactivated the ventral medial prefrontal cortex. Patients failed to deactivate the posterior midline and lateral parts of DMN network. After levodopa administration, this network was restored conjointly with the improvement of motor dysfunction in PD patients. The levodopa effect on DMN is probably the consequence of a beneficial dopamine (DA) medication effect which leads to a fine tuning of the dopamine level in the motor part of striatum, resulting to a global improvement of physical state of PD patients and consequently an increased attentional resource to external stimuli. The absence of medial prefrontal deactivation impairment may suggest a preserved mesocortical DA system in these patients.

* Corresponding author. Emotion Center, Groupe Hospitalier Pitié-Salpétrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France. Tel.: +33 1 42 16 16 55; fax: +33 1 53 79 07 50.
E-mail address: pauline.delaveau@yahoo.fr (P. Delaveau).

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doi:10.1016/j.euroneuro.2010.07.001

1. Introduction

Default mode network (DMN) has been identified from resting states and cognitively simple baseline tasks compared to a variety of more demanding experimental tasks. It encompasses the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), precuneus, lateral parietal and temporal cortices (Raichle et al., 2001; Raichle and Snyder, 2007). These brain areas have been linked to self-oriented mental activity (Harrison et al., 2008; Spreng et al., 2009) and are deactivated during externally goal-directed activity (Gusnard and Raichle, 2001).

The relevance of the DMN dysfunction has been emphasized in several neuropsychiatric diseases particularly mental disorders such as autism, schizophrenia, Alzheimer's disease, depression and attention-deficit/hyperactivity disorder (Buckner et al., 2008; Broyd et al., 2009). Recent studies focused on DMN in Parkinson's disease. However, their findings are contradictory. In unmedicated PD patients, the posterior midline part of DMN failed to deactivate during an executive task (van Eimeren et al., 2009). On the other hand, in medicated PD patients, a failure of deactivation in the ventral MPFC (vMPFC) was found during a sequence learning task (Argyelan et al., 2008) or in both the anterior and posterior parts of this network during the resting state (Tinaz et al., 2008). In a recent study, the DMN was preserved in both OFF and ON dopaminergic treatment during an executive task (Nagano-Saito et al., 2009). The role of dopamine (DA) neurotransmission on DMN in PD remains unclear. Recently, in healthy subjects, an increased dopamine transporter availability (lower dopamine in the synapses) in the striatum was associated with a lower deactivation in the parietal part of DMN (i.e. the precuneus) and a higher deactivation in the ventral anterior cingulate gyrus during a parametric visual attention task (Tomasi et al., 2009). In addition, in healthy subjects, transient dopamine depletion led to a decreased deactivation in DMN during a set-shifting task including the MPFC and the PCC (Nagano-Saito et al., 2008).

Contrary to the previous study investigating the dopaminergic modulation of the brain activation during an emotional task in PD (Delaveau et al., 2009), we focused on brain deactivation during the same task. To assess the dopamine regulation on DMN, we compared the effects of levodopa versus placebo on the brain deactivation in PD patients and the control subjects. We hypothesized that DMN deactivation is altered in PD patients and that dopamine could modulate this task-induced deactivation.

2. Experimental procedures

2.1. Participants

We used the same participant groups in our previous study (Delaveau et al., 2009). Fourteen right-handed patients with PD (3 females and 11 males) aged 42 to 70 (mean age = 61 ± 8.3 years) and thirteen right-handed healthy controls (6 females and 7 males) aged 46 to 80 years (mean age = 56 ± 8.9 years) participated in the study.

The PD patients were recruited from the Movement Disorders neurological department of La Timone hospital after having been selected for surgical treatment of PD (subthalamic nuclei deep brain stimulation). They had a mean score of Hoehn and Yahr stage at 2 (±0.9) and a disease's duration mean of 11.4 years (±4.4). All patients had a Mattis dementia rating scale score >126, (Mattis, 1976), were free of major depressive state (Beck Depression Inventory (BDI) score <16 (Beck and Beamesderfer, 1974) and Montgomery–Asberg Depression Rating Scale (MADRS<21) (Montgomery et al., 1985). They showed no impairment in neurocognitive functions (semantic/verbal fluency, working memory and executive functions).

All control participants were in good health as assessed by a complete medical questionnaire including medical history, a physical examination, and a psychiatric interview. None showed evidence of a demented state (Mini Mental State Examination>24) (Folstein et al., 1975) and none were receiving any psychotropic drugs.

This study was conducted in accordance with the principles of the declaration of Helsinki. Approval was obtained from a local Ethics Committee. Each participant gave his/her informed written consent before entering the study.

2.2. Treatment

Patients were being treated for PD with levodopa alone or in combination with dopamine agonists. In order to avoid different pharmacological effects of DA on brain activity, we administered only oral levodopa (or placebo) to the participants. To provide an optimal therapeutic response for each patient, the morning levodopa equivalent dose was calculated on the basis of corresponding doses of their usual dopamine agonist medications (Lozano et al., 1995; Krack et al., 1998) (mean dose = 300 mg). The PD patients were asked to abstain from their dopaminergic medication at least 12 h before the experiment.

The healthy participants received a single oral dose of either 100 mg of levodopa with 25 mg of benserazide or placebo. In addition, they were treated with 20 mg of domperidone to avoid peripheral side effects.

Treatment was administrated to reach the theoretical plasma peak of medication (Chana et al., 2003) when the participant performed the emotional test.

The study design was a randomized, crossover experiment consisting of two assessments separated by a washout of 1 to 7 days. Each participant was treated with placebo or levodopa, then scanned on two occasions in counterbalanced order.

The treatments (levodopa/placebo) were randomized and identical in appearance (capsules) to blind the participant to treatment. Participants were entered into the study and allocated a subject number according to chronological order of inclusion. They were assigned the corresponding treatment number.

2.3. Clinical scales

Before each session, all participants rated a visual analogue scale comprising three mood factors, alertness, calmness and contentment (Bond and Lader, 1974). Additionally for the patients, the Parkinson's motor symptoms severity was assessed by the third part of the Unified Parkinson's Disease Rating Scale (Fahn et al., 1987).

2.4. Emotional facial matching test

In the emotional task, participants viewed a target face and had to select which of the two faces expressed the same emotion (fear or anger). The face colour photos were derived from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998). In the control task, participants viewed a target oval shape, and chose which of the two ovals matched the target.

2.5. fMRI protocol

A blocked fMRI design was used, consisting of one fourteen blocks (seven emotional blocks and seven control blocks) series. The emotional blocks contained 8 pictures presented for 5 s. The control blocks contained 10 pictures presented for 4 s. The pictures were presented in a pseudorandomized order.

2.6. MRI acquisition

All data acquisition was performed on a 3-T MEDSPEC 30/80 AVANCE imager (Bruker, Ettlingen, Germany). The fMRI scans were acquired using a T2*-weighted gradient-echoplanar sequence (TR/TE = 3000/35 ms; FOV = 19.2 × 19.2 cm, 64 × 64 matrix; flip angle = 90°). 36 interleaved axial slices were obtained with a contiguous slice thickness of 3 mm. The slices covered the whole brain and were acquired parallel to the anterioposterior commissure plane. The sequence lasted 11 min, resulting in 221 images.

A set of high-resolution T1-weighted sagittal images were acquired (TR/TE = 25/5 ms; FOV = 19.2 × 19.2 cm; 256 × 256 matrix, contiguous slices thickness of 1.2 mm); these whole brain data were acquired.

2.7. fMRI data analysis

Data were processed using SPM software (www.fil.ion.ucl.ac.uk/spm). With SPM2, a standard pre-processing of data was performed (slice timing, movement correction, spatial normalization using a binary mask to minimize deformation and spatial smoothing with a kernel of 6 mm).

Individual analyses evaluating differences between the emotional and control conditions were performed. Each condition was modeled by a box-car convolved with a canonical hemodynamic response function. Movement parameters were used as additional regressors in the model when they exceeded 1 mm and/or 1°. Using the appropriate linear contrast (emotional condition: −1; control condition: 1; movement parameters: 0), contrast images were computed for each subject representing BOLD signal decreases in emotional relative to control condition.

We carried out second-level random effects analyses separately for each medication session for each subject group using SPM5. A one-sample *t*-test was performed to assess deactivation-specific regional responses for each group ($p<0.001$). A between-group analysis was performed ('full factorial' SPM5 model). As PD patients differed from healthy participants in term of age ($p=0.045$) and gender (more men in PD group), an analysis of variance comprising a factor group (patients/controls) with two levels (levodopa/placebo) was employed, using both age and gender as covariates of no interest ($p<0.05$ corrected by False Discovery Rate controlling the number of false positives compared to the total number of positives). We focused the analysis on the deactivation network using a mask functionally defined by adding all clusters from the within-group analyses thresholded at *p*-uncorrected <0.001 (size of clusters >20 voxels) of each group to ensure that the chosen regions were linked to the cortical deactivation during the emotional task.

2.8. Behavioral data analysis

Differences in clinical scales and task performance was conducted between control and patient groups were compared using a Student's *t*-test, or a non parametric Mann–Whitney test from the SPSS.

Differences between both drug states for each group were compared using the paired Student's *t*-test, or the non parametric Wilcoxon test for two related samples ($p<0.05$).

3. Results

3.1. Behavioral results

Table 1 summarizes the descriptive results of clinical scales and emotional task performance in both subject groups.

Under placebo, patients showed lower vigilance ($t=-5.76$, $p<0.001$), contentment ($t=-5.76$, $p=0.009$), and calmness ($t=-3.71$, $p=0.001$) compared to control subjects.

For the healthy subjects, there was no mood/vigilance difference between pharmacological states. For the PD patients, the vigilance was lower in the placebo than in the levodopa session ($t=-2.58$, $p=0.023$).

The PD patients' UPDRS motor score was significantly higher (i.e. worse motor function) in the placebo than the levodopa session ($t=11.01$, $p<0.001$).

In emotional task, the accuracy mean was not different between subject groups (controls > patients, placebo: $t=1.3$, $p=0.23$; levodopa: $t=1.3$, $p=0.20$) or between pharmacological state in either group (placebo > levodopa, patients: $t=0.54$, $p=0.60$; healthy subjects: $Z=1.07$, $p=0.29$).

3.2. fMRI results

Regarding brain deactivation results, healthy subjects showed a decrease of BOLD signal in the MPFC, anterior, mid-anterior and posterior cingulate gyri, parts of lateral parietal and temporal cortices, and the right precentral gyrus in response to emotional compared to control task in both pharmacological conditions (Fig. 1A, Table 2a and b).

Patients with PD only showed a deactivation in the MPFC in the placebo condition. A decreased activity in the PCC, lateral temporal cortex and left pre/postcentral gyrus was found after levodopa administration (Fig. 1B, Table 2c and d).

To explore the possible influence of both covariates of no interest (age and gender) on brain deactivation, we computed

Table 1 Descriptive results (mean ± standard deviation) of the clinical scales and the emotional task performance in the controls and PD patients for both medication conditions.

	Controls		Patients	
	Placebo	Levodopa	Placebo	Levodopa
Vigilance, % (SD)	83.2 (10.6)	82.8 (11.4)	51.9 (16.7)	65.6 (17.4)
Calmness, % (SD)	88 (13.2)	84.5 (15.1)	57.6 (15.3)	65.1 (19)
Contentment, % (SD)	85 (13.4)	86 (12.9)	66 (14.6)	74.4 (13.9)
UPDRS III, mean (SD)	–	–	22 (6.8)	6.7 (3.1)
Task performance, % correct responses (SD)	93.8 (5.2)	93.4 (4.8)	89.2 (13)	88.9 (10.7)

SD = standard deviation.

F-contrasts in the analysis of variance model to look for the main effects of age and gender. None effect was revealed for both covariates (p-uncorrected<0.001). The comparison between the controls and PD patients in placebo condition revealed more deactivation in the posterior and mid-anterior cingulate cortices, precuneus, bilateral precentral gyrus, left lateral parietal and bilateral lateral temporal cortices in controls. The opposite comparison (patients>controls) revealed no difference in brain deactivation (Table 3). When the PD patients took the levodopa medication (controls with placebo>patients with levodopa), we only found the precentral gyrus (Talairach's coordinates: 55 −3 19, t=4.7) more deactivated in controls than in patients.

In the control group, no treatment effect was found in the levodopa>placebo condition. Only the right precentral gyrus (Talairach's coordinates: 55 −3 19, t=6.2) was found more deactivated in placebo compared to levodopa condition.

The PD patients showed a higher deactivation in the PCC and precuneus (BA 31), bilateral precentral gyrus and bilateral lateral temporal cortex in the levodopa compared to placebo session. The opposite comparison (placebo>levodopa) revealed no difference in brain deactivation (Table 4).

An interaction between groups (patients/controls) and medications (levodopa/placebo) was found in several areas such as the posterior and mid-anterior cingulate cortices, right precentral gyrus, left lateral parietal and bilateral temporal gyri (see Fig. 2, Table 5).

4. Discussion

In our study, we assessed the functional integrity of DMN in Parkinson's disease and the dopaminergic modulation of this network by investigating the brain deactivation during an emotional task in non-demented and non-depressed PD patients and healthy subjects with and without levodopa medication. In control subjects, we found a classical brain deactivation network during the goal-directed task, including the anterior and posterior midline parts of DMN, respectively the vMPFC and the PCC, in placebo and levodopa medication conditions. First, it is interesting to highlight the robustness of DMN deactivation in response to a large sample of external attention-demanding tasks, i.e. during cognitive as well as emotional tasks.

Under placebo, the comparison between both subject groups revealed that the PD patients failed to deactivate the posterior midline and lateral parts of the brain deactivation network. After levodopa administration, DMN was restored in PD patients.

Our findings suggest impairment to deactivate DMN during an emotional task in the PD patients without dopaminergic medication. The improvement of DMN deactivation after levodopa administration concomitantly with the improvement of motor function and vigilance of PD patients could reflect a global beneficial DA effect on their general state and their alertness correcting the low level of DA in the basal ganglia. In off-levodopa situation, sensory symptoms (i.e. diffuse pain), autonomic symptoms (i.e. sweating) or fatigue are frequently reported by PD patients and relieved by dopaminergic therapy (Cheon et al., 2009). For example, pain perception involves the activation of several brain regions including the mid-anterior cingulate, PCC, posterior parietal and somatosensory cortices (pre/postcentral gyri) (Apkarian et al., 2005). This could explain the non-deactivation of these regions normally found during this emotional task in the controls. These physical (internal)

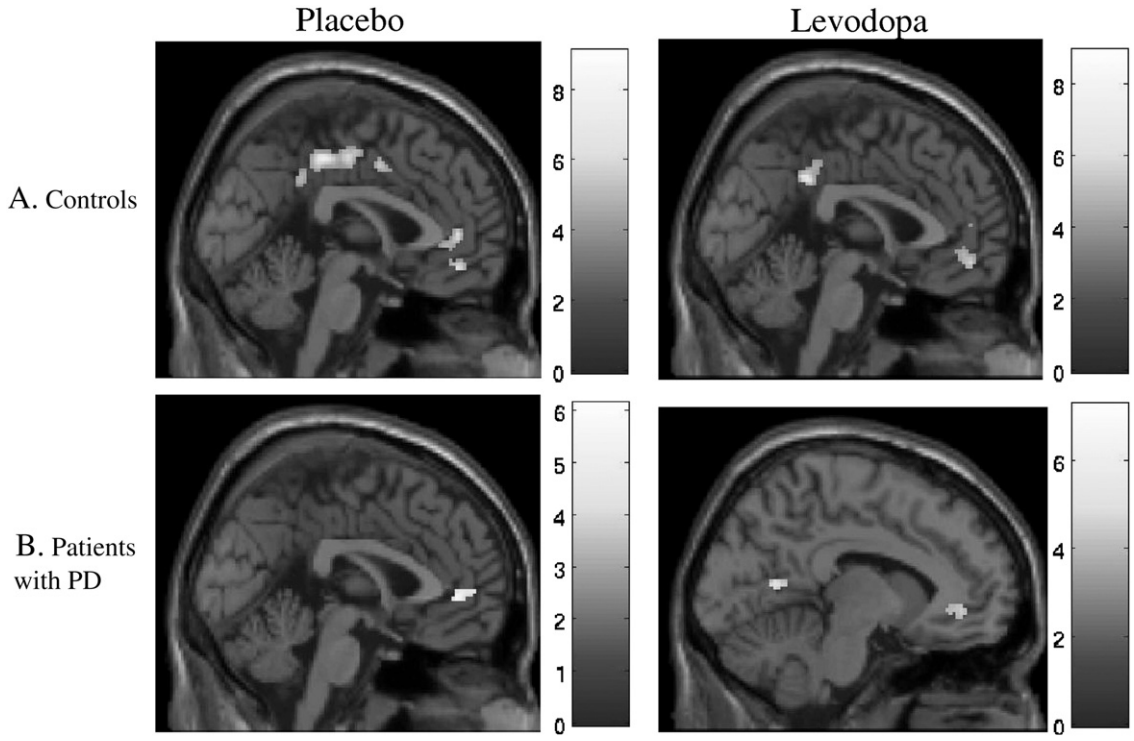

Figure 1 Pattern of deactivations in medial prefrontal and cingulate cortices during emotional relative to control tasks for controls and PD patients in each medication (placebo/levodopa).

Table 2 Brain deactivations during emotional relative to control condition in the controls and patients for both medication conditions (all $p<0.001$ uncorrected, number of voxels>20 per cluster). *$p<0.05$ corrected at cluster level.

Brain regions (right: R, left: L)	Talairach's coordinates (mm)			T value	Z score
	x	y	z		
a) CONTROLS placebo					
Medial frontal gyrus BA11	0	42	−12	6.2*	4.1
Anterior cingulate BA32	4	41	2	6.2*	4.1
Cingulate gyrus BA24	8	−8	39	6.6	4.2
BA24	0	2	39	5.3*	3.8
BA31	−2	−29	44	7.7*	4.5
Precuneus BA31	−2	−43	33	5.3	3.7
Superior temporal gyrus BA42 R	57	−30	16	9.1*	4.9
Superior temporal gyrus R	53	5	−7	5.6	3.8
Insula/superior temporal gyrus L	−46	−17	10	9.1*	4.9
Superior temporal gyrus BA39 L	−53	−61	29	5.6	3.9
Insula R	34	8	3	7.4	4.5
Parahippocampal region L	−40	−16	−11	5.3*	3.8
Precentral/postcentral gyrus L	−48	−17	38	7.5*	4.5
Precentral gyrus R	57	−2	37	6.7	4.3
b) CONTROLS levodopa					
Medial frontal gyrus BA10	−6	51	3	5.3	3.7
Medial frontal gyrus BA 10/ anterior cingulate gyrus BA32	−10	48	−9	7.1*	4.4
Cingulate gyrus BA31/ precuneus	−2	−39	33	8.9*	4.9
Cingulate gyrus	−8	−31	38	5.1	3.6
Posterior cingulate BA23	−8	−57	21	6.7*	4.2
Superior parietal lobule BA5 R	24	−40	61	5.7	3.9
Inferior parietal lobule BA40 R	53	−32	22	5.6*	3.9
Precuneus BA39 L	−44	−72	37	5.9	4
Postcentral gyrus BA3 L	−55	−10	24	6.4	4.2
Precentral gyrus BA4 R	63	−1	17	6.8	4.3
Insula BA13 R	36	−19	16	5.4	3.8
Insula BA13 R	40	−17	3	5.1	3.7
Insula BA13 L	−38	−17	8	4.8	3.5
c) PATIENTS placebo					
Anterior cingulate BA32/ medial frontal gyrus BA10	−4	44	2	6.1*	4.1
d) PATIENTS levodopa					
Anterior cingulate BA32/24	2	43	−5	5.7*	4
Posterior cingulate BA30	−8	−59	12	5.3	3.8
Superior temporal gyrus L	−55	0	2	6	4.1
Superior temporal gyrus BA41 R	49	−29	12	5.2	3.8
Temporal lobe L	−32	−64	7	6	4.1
Temporal lobe R	40	−8	−11	5.6*	3.9
Precentral gyrus (BA4)/ postcentral gyrus (BA40) L	−55	−28	27	7.3*	4.5

Table 3 Difference of brain deactivations during emotional relative to control condition between both subjects groups (all $p<0.05$ FDR-corrected, number of voxels>20 per cluster). *$p<0.05$ corrected at cluster level.

Brain regions (right: R, left: L)	Talairach's coordinates (mm)			T value	Z score
	x	y	z		
a) CONTROLS(placebo)>PATIENTS(placebo)					
Cingulate gyrus BA31	−4	−29	40	4.7*	4.2
Precuneus BA31	−6	−47	34	3.9	3.6
Posterior cingulate BA29	−6	−50	10	3.5	3.3
Cingulate gyrus BA24	−8	9	35	4.9	4.4
Precentral gyrus BA4/6 R	55	−3	19	7	5.8
Precentral gyrus BA6 R	57	−6	37	5	4.4
Precentral gyrus BA4 L	−53	−10	26	4	3.7
Postcentral gyrus BA3 L	−48	−15	47	4.4	4
Inferior parietal lobule BA40 L	−59	−34	27	2.9	
Angular gyrus BA39/ supramarginal gyrus BA40 L	−53	−57	34	3.8	3.5
Superior temporal gyrus BA22/ 41L	−49	−33	5	5.6	4.9
Superior temporal gyrus/insula BA13 R	−51	−15	6	3.9	3.6
Superior temporal gyrus R	−44	−14	−3	3.5	3.2
Insula BA13 L	38	−21	5	3.4	3.2
	57	−11	8	2.9	2.8
	−38	−21	−1	3.4	3.2
b) PATIENTS(placebo)>CONTROLS(placebo)					
	No significant clusters				

Table 4 Difference of brain deactivations during emotional relative to control condition between both medications in PD patients ($p<0.05$ FDR-corrected, size of clusters>20 voxels).

Brain regions (right: R, left: L)	Talairach's coordinates (mm)			T value	Z score
	x	y	z		
a) PATIENTS levodopa>placebo					
Cingulate gyrus BA31	−6	−31	37	4.7	4.3
Cingulate gyrus/precuneus BA31	−8	−43	35	3.4	3.2
Precentral gyrus BA6 R	51	−3	19	4.9	4.3
Precentral gyrus BA4 L	−49	−12	26	4.4	4
Insula L	−38	−23	−3	4.2	3.9
Superior temporal gyrus R	46	−23	9	3.8	3.5
b) PATIENTS placebo>levodopa					
	No significant clusters				

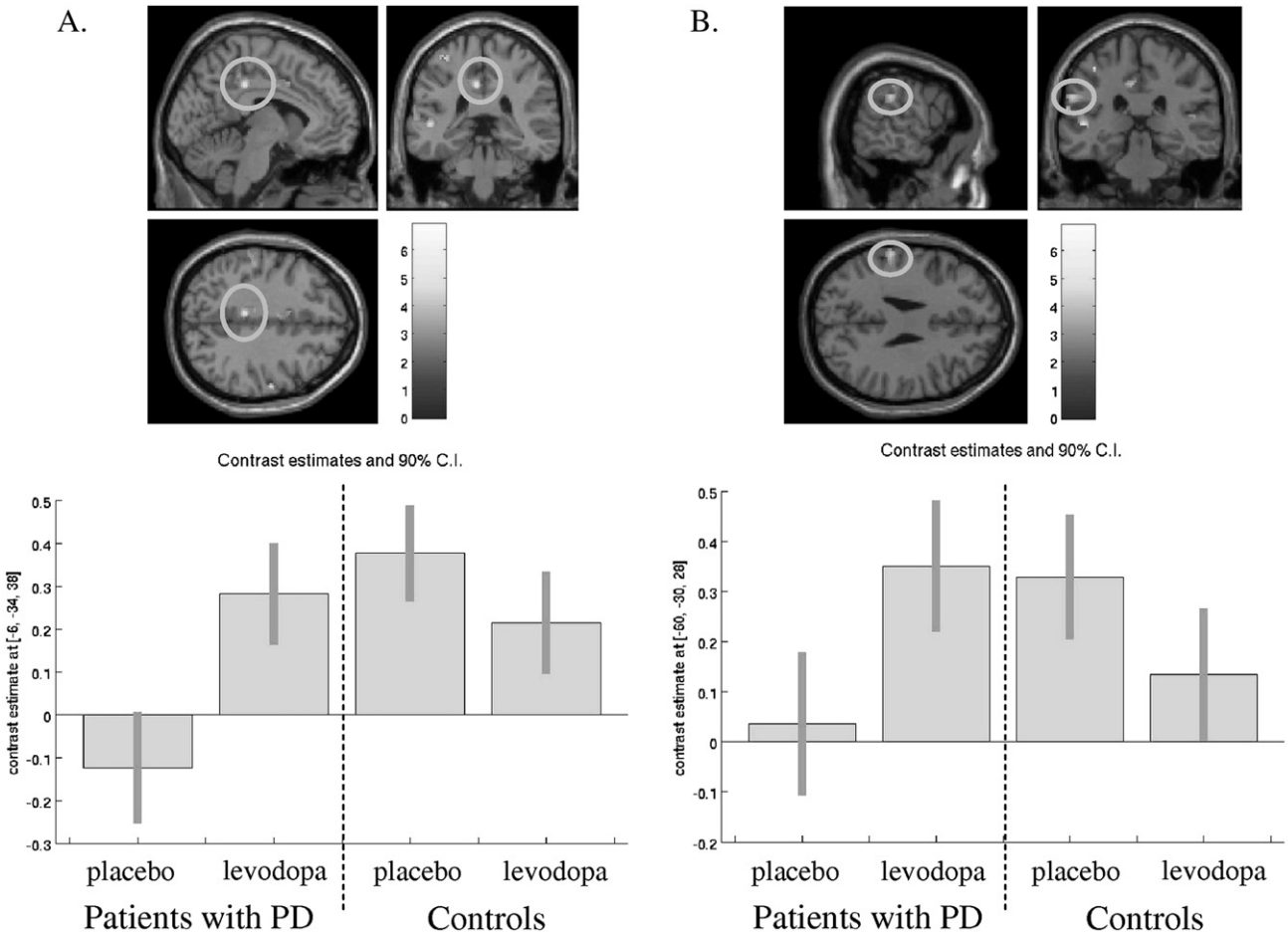

Figure 2 Deactivation interactions between subjects groups (patients/controls) and medications (levodopa/placebo) within the PCC (A) and inferior parietal lobule (B). The bar graphs plot the contrast estimates per group and medication.

Table 5 Brain deactivations interactions between subjects groups (patients/controls) and medications (levodopa/placebo) ($p<0.05$ FDR-corrected, size of clusters>20 voxels).

Brain regions (right: R, left: L)	Talairach's coordinates (mm)			T value	Z score
	x	y	z		
Cingulate gyrus/precuneus BA31	−6	−31	37	5.1	4.5
Cingulate gyrus BA24	−2	2	40	3.6	3.4
Precentral gyrus BA6 R	53	−3	19	6.9	5.7
Postcentral gyrus L	−40	−27	51	4.7	4.3
Postcentral gyrus/Inferior parietal lobule	−65	−24	18	4.4	4
BA40 L	−49	−22	36	3.6	3.4
Inferior parietal lobule BA40 L	−59	−28	27	4.1	3.8
Superior temporal gyrus BA22 L	−49	−31	5	5	4.5
Insula R	38	−16	−8	3.5	3.2
Transverse temporal gyrus BA41 R	46	−23	10	3.2	3

sensations linked to disease may impair DMN deactivation by affecting the availability of attentional resources to external stimuli.

This impairment of brain deactivation was not found in the anterior part of DMN. This present result is concordant with the previous study of van Eimeren et al. (2009) showing a failure of brain deactivation during an executive task in the PCC and the precuneus but not in the MPFC in PD patients not taking DA medication. In addition, our findings highlighted the restoration of the posterior midline deactivation by DA medication. In our previous study on dopaminergic modulation of amygdala activity in the same PD patients' sample, we found the same levodopa effect on amygdala activation in PD patients and control subjects. We interpreted this result as supporting the hypothesis that the ventral tegmental area, the origin of mesolimbic DA projections to the amygdala, was relatively preserved to DA depletion compared to the dorsal striatal denervation in these patients (Delaveau et al., 2009). The DA projection from the ventral tegmental area to prefrontal cortex (mesocortical DA system) is also well known (Fluxe et al., 1974). Consequently, the unimpaired MPFC deactivation in these PD patients could be explained by the preserved mesocortical DA projections. It is difficult to make comparisons with the previous studies on DMN in PD because of a lack of several clinical criteria specified in some studies which could suggest differences of DA depletion and

hence explain the discrepancy between the prior results (i.e. PD duration, impairment in prefrontal cognitive functions, presence of depression). However, similar to our study, the PD patients showing an unimpaired prefrontal deactivation in off-treatment condition were non-demented, non-depressed and without clinically overt executive deficits, mediated by the frontal lobe (van Eimeren et al., 2009). Moreover, a hypoactivation of DMN during a resting state (for both anterior and posterior parts) was found in PD patients with frontal-executive function deficits (with DA medication, there was not an off-treatment condition in this study) (Tinaz et al., 2008).

A recent study in patients with schizophrenia showed a negative correlation between physical anhedonia scores and resting state metabolic activities in the ventral prefrontal cortex (Park et al., 2009). Anhedonia is a component of negative symptoms in Schizophrenia that have been linked to alteration in the DA mesocortical system (Abi-Dargham, 2004).

In non-pathological conditions, the activities of DMN, notably the posterior and anterior parts, are positively correlated, i.e. they are activated together at rest and they deactivate together in goal-directed tasks. However, in several disorders other than PD such as Alzheimer's disease, schizophrenia, autism spectrum disorders or epilepsy, a disruption of the functional connectivity between these regions at rest were found (Buckner et al., 2008; Broyd et al., 2009). Also, some goal-directed task studies showed the absence of deactivation of one part of midline structures. For example, during an n-back task, a failure to deactivate the MPFC was evidenced in patients with schizophrenia, (Pomarol-Clotet et al., 2008). Likewise during a face perception task, patients with social phobia showed a lower deactivation in precuneus and PCC than controls (Gentili et al., 2009). Overall, the previous findings and the present results underline the involvement of dissociation between the anterior and posterior parts of DMN in several psychiatric and neurological disorders. Interestingly, a recent resting state study individually assessed functional connectivity of the vMPFC and PCC (Uddin et al., 2009). In addition to the positively correlated common networks for both midline DMN parts, dissociable anticorrelated networks associated with the anterior and posterior seeded regions were evidenced. Whereas the vMPFC negatively correlated with activity of visual and spatial attention networks, the PCC negatively correlated with the activity of prefrontal-based motor control circuits. In the present study, we hypothesise that the impaired deactivation of the PCC in PD patients would be the indirect consequence of the nigrostriatal DA denervation on the putamen being part of the motor basal ganglia-thalamo-cortical circuit (Alexander et al., 1990).

The failure to deactivate DMN in the PD patients taking placebo did not affect performance in the emotional task compared to control subjects. A difference of brain activation concomitantly with an absence of behavioral difference between PD patients and controls was previously found in the same task (Tessitore et al., 2002). The ease of performing this task could lead to a ceiling effect explaining the lack of difference between placebo and levodopa on task performance. An alternative explanation may be a compensatory effect by the activation or the "non-deactivation" of DMN during the emotional goal-directed task in the PD patients not taking levodopa. Further studies should focus on spontaneous resting state, a more unconstrained assessment, in PD to investigate the functional connectivity of DMN without task performance constraint.

The present study had several limitations. First, the number of patients and controls included is relatively small. Second we used a marginal external attention-demanding task to investigate DMN deactivation. So the generalization of the present findings is limited. Moreover, patients and controls had a different age and gender distribution. A decreased deactivation of DMN has been shown in older subjects (>60 years), with more significance when the cognitive load of the task increases (Sambataro et al., 2008; Persson et al., 2007). However, an absence of age differences on DMN deactivation in tasks with minimal selection demands was reported (Persson et al., 2007). As seen above, the emotional task used in the present study was easy to perform. Besides, DMN seems to be very little sensitive to a sex effect. One study investigated the possible sex difference in DMN connectivity. The authors underlined that the sex effect was quite small relative to overall default mode network connectivity. They found a higher connectivity between PCC/precuneus and medial prefrontal cortex and a higher activity of superior frontal gyrus at rest in female participants (Bluhm et al., 2008). Any case, to limit potential bias due to these factors, we included age and sex as covariates of no interest in between-groups comparison analysis. However, further studies with larger samples without a difference of age and gender would be desirable. Finally, another limitation is to have performed the pre-processing of fMRI data using SPM2. The procedures of fMRI pre-processing improve according to new versions of SPM. In particular, the normalization procedure in SPM2 (including global linear and local non linear transformations) is less accurate than SPM5 (including a probabilistic framework, which integrates image registration, tissue classification, and bias correction within the same generative model).

In summary, our brain deactivation findings during a goal-directed task evidenced dysfunctions of DMN, except in the anterior part, in non-demented, non-depressed PD patients without DA medication. The levodopa medication restored an optimal DMN deactivation in particular in the PCC/precuneus. This influence of DA medication on DMN is probably due to a fine tuning of the dopamine level in the motor part of the striatum, resulting to a global improvement of physical state of PD patients and consequently an increased attentional resource to external stimuli. The absence of MPFC deactivation impairment may indicate a preserved mesocortical DA system in these patients.

Role of the funding source

This study was supported by a grant from the Health Ministry, Hospital Protocol of Clinical Research (PHRC 2001). PD is supported by Institut de Recherches Internationales Servier (IRIS). These fundings had no further role in the study design; in the collection, the analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

OB and JPA: overall concept, design of the study, writing of the protocol, general coordination. JPA and TW: patients' recruitment and critical revision of document. PD: data acquisition, writing of the first draft of the manuscript. PD and PSP: statistical analysis, interpretation of results and critical revision of document. OB and PF: managing of the literature searches, interpretation of results and critical revision of document. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors reported no biomedical financial interests or potential conflict of interest.

Acknowledgements

The authors thank Catherine Cassé-Perrot and Marie Delfini for neuropsychological assessment of the PD patients. They thank Dr Jean-Luc Anton, Dr Bruno Nazarian and Dr Muriel Roth of "Centre IRMf de Marseille" for technical assistance. Finally, they thank Albert Moukheiber for the correction of the English text.

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