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### ► To cite this version:

Karel Joineau, Mathilde Boussac, Patrice Peran, David Devos, Jean Luc Houeto, et al.. Parkinsonian central pain is linked to the connectivity of the nucleus accumbens and the anterior insula. *Neuroimage: Reports*, 2024, 4 (1), pp.100197. 10.1016/j.ynirp.2024.100197 . hal-04473932

**HAL Id: hal-04473932**

**<https://u-picardie.hal.science/hal-04473932>**

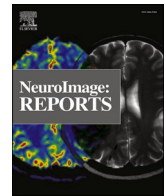
Submitted on 24 May 2024

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## Parkinsonian central pain is linked to the connectivity of the nucleus accumbens and the anterior insula

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### ARTICLE INFO

#### Keywords:

Parkinson's disease  
Pain  
Resting state  
Functional connectivity  
Levodopa  
Oxycodone

### ABSTRACT

Pain is a frequent and disabling non-motor symptom of Parkinson's Disease (PD). Yet, no treatment to date can efficiently reduce this pain. This article investigates the brain functional connectivity of PD patients with central pain and the effects of levodopa and oxycodone on this connectivity.

Thirty-eight PD patients received either levodopa, oxycodone, or a placebo during an eight-week period. Pain intensity was evaluated using the Visual Analogue Scale and resting-state functional connectivity was measured before and after treatments. PD patients were also separated into two groups: responders and non-responders.

At baseline, the intensity of pain was correlated with the connectivity between the anterior insula and the posterior cingulate cortex and between the nucleus accumbens, the brainstem, and the hippocampus. Levodopa and oxycodone had no specific effects on functional connectivity. Responders had a decrease in connectivity between the anterior insula and the posterior cingulate cortex, while non-responders showed an increase in connectivity.

The correlation between pain intensity and specific brain connectivity may represent a "hyper-awareness" of pain and a distortion of learning and memory systems in PD patients with central pain, leading to a state of

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<https://doi.org/10.1016/j.ynirp.2024.100197>

Received 18 August 2023; Received in revised form 18 December 2023; Accepted 17 January 2024

Available online 2 February 2024

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chronic pain. The placebo effect could explain the changes in connectivity that are associated with a potential reduction in pain awareness.

## 1. Introduction

The main markers of Parkinson's Disease (PD) are the degeneration of dopaminergic neurons and the pathological deposition of  $\alpha$ -synuclein (Dickson et al., 2009), which cause motor symptoms such as bradykinesia, hypertonia, and resting tremor (Kalia and Lang, 2015), as well as non-motor symptoms such as neuropsychiatric disorders, sleep disorders, neuro-vegetative symptoms, and pain (Schapira et al., 2017).

Pain is one of the most disabling non-motor symptoms of PD, impacting between 40 and 80 % of PD patients (Beiske et al., 2009; Defazio et al., 2008; Negre-Pages, 2008) and impairing their quality of life (Antonini et al., 2018; Choi et al., 2017).

A classification of PD pain, based on its underlying physiological mechanisms, has recently been established, which categorises pain as nociceptive, neuropathic, or nociplastic, depending on the cause of the pain either specific or non-specific to PD (Marques et al., 2019; Mylius et al., 2021). Non-specific pain was defined as musculoskeletal pain, radicular pain, and restless leg syndrome; and pain specific to PD can be nociceptive, like dystonia, or can be nociplastic, such as parkinsonian central pain (Marques et al., 2019; Marques and Brefel-Courbon, 2020). Parkinsonian central pain is thought to result from a dysfunction of the central somatosensory system and is not sufficiently explained by rigidity, dystonia, or lesions in muscles, bones, or organs. It can take many clinical forms, such as burning, tingling, bizarre, and unexplained sensations. According to the literature, the prevalence of this type of pain varies from 10 % to 28 % (Beiske et al., 2009; Defazio et al., 2008; Ghosh et al., 2020; Silverdale et al., 2018; Valkovic et al., 2015).

Pharmacological drugs could therefore be effective in treating PD pain. The first strategy would involve optimising the dosage of dopamine, since PD is characterised by a lack of dopamine in the basal ganglia, which is a relay of nociceptive information (Edinoff et al., 2020). Indeed, the administration of levodopa, the gold standard of anti-parkinsonian treatment, has been shown to raise pain thresholds in PD patients (Brefel-Courbon et al., 2005, 2013). However, no clinical study to date has evaluated the effect of levodopa on clinical pain, especially central pain. Conventional analgesics such as opioid drugs could also be used. In a multicentre, double-blind, randomized, placebo-controlled trial, a combination of oxycodone and naloxone showed a significant but transient decrease in chronic pain in PD patients (Trenkwalder et al., 2015). But the effect of oxycodone on the different types of PD pain has still not been studied.

Neuroimaging can help us to understand the pathophysiology of pain in PD. Undergoing brain Positron Emission Tomography (PET) in an experimental nociceptive stimulation, patients with central PD pain showed an overactivation of neural pain areas associated with the emotional component of this pain (posterior insula, occipital cortex and anterior cingulate cortex) when compared to PD pain-free patients, who, in turn, presented increased activation in nociceptive areas associated with its sensitive components (Brefel-Courbon et al., 2013).

Resting-state functional Magnetic Resonance Imaging (rs-fMRI) studies have shown regional disturbances in some pain-related areas such as the orbitofrontal cortex, the cerebellum, and some temporal areas in PD patients with pain that are not present in PD patients without pain (Polli et al., 2016). Moreover, in comparison with healthy subjects, PD patients with pain had a decrease of connectivity between the nucleus accumbens and the hippocampus (Polli et al., 2016). There was a positive correlation between pain intensity and the connectivity of the accumbens with the primary motor cortex and the sensory areas in PD patients (Kinugawa et al., 2022). Furthermore, in patients with chronic pain, pain relief was predicted by the positive connectivity between the medial prefrontal cortex and the insula (Tu et al., 2019). However, the

different types of pain in PD have never been specified in these functional connectivity studies.

The aim of this study was to investigate the effects of levodopa and oxycodone on functional connectivity in PD patients with specific central pain within three seeds: the insula, the accumbens, and the medial prefrontal cortex, and within the Default Mode Network (DMN). Our hypotheses were that: 1) the functional connectivity of these three seeds would be linked to the intensity of pain; 2) levodopa and oxycodone would induce specific changes within these connectivities; and 3) changes in functional connectivity would differ between patients according to their responses to treatments or a placebo.

## 2. Materials and methods

This study was part of the OXYDOPA study (ClinicalTrials.gov Identifier: NCT02601586), a randomised clinical trial that sets out to investigate the effects of oxycodone and levodopa on central Parkinsonian pain. It is sponsored by the University Hospital of Toulouse, conducted in fifteen centres with expertise in PD in the clinical research network in France (NS-Park/F-Crin), and was approved by the CPP Sud-Ouest et Outre-Mer III Ethical Committee August 26, 2015 (n°2015/55).

### 2.1. Patients

Our inclusion criteria were: idiopathic PD according to the criteria of the United Kingdom PD Society's Brain Bank; and the presence of central pain for at least 3 months and with an intensity greater than 3 points on the Visual Analogue Scale (VAS > 3).

Parkinsonian central pain was defined: 1) as pain related to PD characterised by the presence of a chronological link (pain occurring at the onset of PD or influenced by a motor condition, mainly during off period), a topographical link (pain located in the half of the body most severely affected by PD), and the lack of other evident painful conditions (rheumatic, traumatic, or orthopaedic disorders) (Dellapina et al., 2012); and 2) based on exclusion criteria (Marques et al., 2019) (were excluded patients with musculoskeletal pain, radicular pain, restless leg syndrome and dystonic pain).

Patients with atypical parkinsonian syndrome, without any dopaminergic treatment, with cognitive impairment (Minimal Mental State Examination [MMSE] < 25), with intercurrent acute pain, or with another chronic disease causing pain were excluded. This study was carried out in accordance with Declaration of Helsinki. All the patients gave their written and oral consent. Their rights to privacy were observed throughout the study.

### 2.2. Study design

The main objective of the OXYDOPA study was to evaluate the respective effects of two pharmacological drugs, oxycodone and levodopa, administered over a period of 8 weeks, versus placebo, on central PD pain intensity. The objective of this exploratory study, ancillary to the OXYDOPA study, was to evaluate the resting-state brain network (3T fMRI) in patients with central PD pain and the respective effects of oxycodone and levodopa, versus placebo, on resting-state brain network changes in order to identify the pathophysiological mechanisms underlying the analgesic effect of each drug.

PD patients were randomly divided into three equal groups according to whether they would be treated by placebo, by up to 200 mg/day of levodopa, or up to 40 mg/day of oxycodone over a period of 8 weeks, in addition to their usual antiparkinsonian treatment. The randomisation list was established by the Methodology and Data Management

department at Toulouse University Hospital using STATA® Version 11.0 (StataCorp LP, College Station, TX 77845 USA, [www.stata.com](http://www.stata.com)).

As this was an exploratory study, only the first 15 patients in each group were able to undergo an MRI examination.

Pain intensity was evaluated using the mean VAS (mean intensity of pain through the past seven days) and the maximal VAS (maximal intensity of pain through the past seven days) before (at baseline) and after 8 weeks of treatment. Different modalities of pain were also evaluated using the McGill Pain Questionnaire (MPQ), the Brief Pain Inventory (BPI), and the King's Parkinson Pain Scale (KPPS). Other clinical parameters were collected: motor state (with the MDS-UPDRS III, Movement Disorder Society – Unified Parkinson's Disease Rating Scale part III); anxiety-depressive state (Hospital Anxiety and Depression [HAD]); quality of life (Parkinson's Disease Questionnaire 39 items [PDQ-39]); sleep (Pittsburgh Sleep Quality Index [PSQI]); and fatigue (Fatigue Severity Scale [FSS]). Levodopa Equivalent Daily Dose (LEDD) was calculated at baseline (Tomlinson et al., 2010).

MRI investigations were performed before and after 8 weeks of treatment.

### 2.3. Image acquisition

Image acquisition included structural (T1) and resting-state functional imaging (rs-fMRI). The acquisition protocol was based on that used in a study by Jovicich et al. (2016) and has been adapted for use in multicentric studies.

Parameters were set identically in all sites, as follows:

For T1 images: MPRAGE sequences were conducted for Siemens and Philips MRI, IR-SPGR for GE MRI with a 3D sagittal acquisition, square FOV = 256 mm,  $1 \times 1 \times 1 \text{ mm}^3$ , TR/TI = 2300/900 ms, flip angle = 9°, no fat suppression, full k-space, no averages.

For functional images: EPI sequences were conducted with a nominal voxel size of  $3 \times 3 \times 3 \text{ mm}^3$ , TE = 30 ms, TR = 2.7 s,  $\alpha = 85^\circ$  (Ernst angle), bicommissural orientation with interleaved slice order (equidistant on Philips, default interleaved on GE and Siemens), 0.45 mm slice gap, 40 slices, 200 vol, and no parallel imaging. The TR was set to the smallest common value attainable across all scanners. Acquisition time was 9 min. Scans were acquired in the ON condition and participants were instructed to relax, keep their eyes closed and try to avoid thinking about anything at all.

### 2.4. rs-fMRI data pre-processing

Data were pre-processed using SPM (<http://www.fil.ion.ucl.ac.uk/spm/>) and the CONN toolbox version 21.a (<http://www.nitrc.org/projects/conn>) (Whitfield-Gabrieli and Nieto-Castanon, 2012). First of all, the functional data were realigned: all scans were co-registered and resampled to a reference image. Following this, any temporal misalignment between different slices was corrected. Outlier scans were identified from the global Blood Oxygen Level Dependant (BOLD) signal and the amount of subject-motion in the scanner and were removed from the data. Functional and anatomical data were then normalised into standard Montreal Neurological Institute (MNI) spaces and segmented into grey matter, white matter, and Cerebral Spinal Fluid (CSF) tissue classes. Lastly, functional data were smoothed using spatial convolution, with a Gaussian kernel of 8 mm full-width half-maximum (Nieto-Castanon, 2020). After this last step, potential confounding effects on the estimated BOLD signal were estimated and removed separately for each voxel and for each subject and functional run using the aCompCor method (Behzadi et al., 2007), including noise components from cerebral white matter and cerebrospinal areas, estimated subject-motion parameters, identified outlier scans or scrubbing, and constant and first-order linear session effects. The residual BOLD time series were then band-pass filtered over a low-frequency window of interest ( $0.009 \text{ Hz} < f < 0.08 \text{ Hz}$ ). Quality control plots of the denoising process were analysed prior to first level analysis.

### 2.5. Seed-to-voxel analyses

Three cerebral areas, which have a major role in parkinsonian chronic pain, were selected for analyses: the insula, the accumbens, and the medial frontal cortex (Baliki et al., 2006, 2012; Kinugawa et al., 2022; Tu et al., 2019). The left and right insulae were separated into their anterior and posterior parts (MNI right posterior insula: +39 -15 +08, left posterior insula: -39 -15 +01, right anterior insula: +32 +16 +6, left anterior insula: -32 +16 +6) (Vogt et al., 2016). The left and right nuclei accumbens were extracted from the Harvard-Oxford atlas directly implemented in CONN. And coordinates established by Baliki et al. (2012) were used for the medial frontal cortex.

In the first level analyses, Pearson's coefficients between the seed's time course and the time courses of all the other voxels of the brain were calculated and converted to normally distributed scores using Fischer transformation. A general linear model was then computed in order to test statistical hypotheses in the second level analyses. For clustering, Gaussian Random Field theory method was used with a cluster threshold corrected for multiple comparisons ( $p < 0.05$ ).

### 2.6. ROI-to-ROI analyses

We have chosen to explore the DMN from the Willard atlas (Richiardi et al., 2015; Shirer et al., 2012) first to verify its presence in our sample of patients to validate the reliability of our functional connectivity data. Then, we explored the effects of the treatments on the DMN functional connectivity, as a second step. For each Region of Interest (ROI), a representative BOLD time course was obtained by averaging the signals of all the voxels within the ROI. For each pair of ROIs, Pearson's coefficients were calculated between their time courses and converted to normally distributed scores using Fischer's transformation. We then applied a general linear model as a second-level analysis.

For clustering, we used the functional network connectivity method described by Jafri et al. (2008), using multivariate statistics to investigate the differences in connectivity between our groups and visits. We used a cluster threshold ( $p < 0.05$ ) corrected for multiple comparisons and an uncorrected connection threshold ( $p < 0.05$ ).

### 2.7. Statistical analyses

**Population.** The normality of the data was evaluated using Shapiro tests. We then drew comparisons of the clinical and connectivity variables between the three treatment groups. We employed ANOVAs for the parametric variables and Kruskal-Wallis tests for the non-parametric ones. A chi2 test was used to compare the qualitative variable (sex) in the three treatment groups.

**Relationship between pain and resting-state connectivity in Seed-to-Voxel analyses at baseline.** To evaluate links between pain intensity and resting state connectivity, we performed Pearson analyses of the correlations between the mean VAS scores and the functional connectivity measures in the Seed-to-Voxel analyses, from the three ROIs previously selected (the insula, the accumbens, and the medial frontal cortex).

**Effects of the treatments on resting-state connectivity.** To evaluate the effects of the treatments on clinical parameters and on resting-state connectivity, we performed  $2 \times 3$  repeated measure ANOVAs with groups of treatments and visits (before and after treatment) as factors on functional connectivity measures from Seed-to-Voxel analyses and on clinical scores. We included the following assessments: mean VAS; maximal VAS; MPQ; BPI; KPPS; MDS-UPDRS III; HAD; PDQ-39; PSQI; and FSS. We assessed the consistency between the VAS score and the patient's interview (improvement, worsening or no change in pain) for each patient.

**Changes in connectivity among the responder and non-responder groups.** To define the two groups, we used the median percentage change of VAS scores (before and after 8 weeks of treatment)

regardless of treatment group. First, we calculated the percentages of pain change for all patients using the mean VAS scores ((pain intensity after treatment – pain intensity at baseline)/pain intensity at baseline). We then calculated the median of these pain change percentage values, after which we divided the patients into two equal groups according to this median. The patients with the lower pain change score were classified into non-responders and the patients with greater pain reduction were classified as responders. The clinical parameters of the two groups were compared using two-sample t-tests of Student or Wilcoxon tests, according to the normality of the data. Patients presenting incoherencies between VAS evaluation and clinical examination were excluded from analyses.

The changes in connectivity values between the two groups were assessed using a  $2 \times 2$  repeated measure ANOVA with groups and visits (before and after treatment) as factors on Seed-to-Voxel connectivity measures. Spearman correlations, between connectivity changes and clinical scores changes, were evaluated to verify that these modifications in connectivity were specific to the evolution of pain intensity.

**ROI-to-ROI analyses in the DMN.** In ROI-to-ROI analyses, the presence of the DMN was verified using a one-sample t-test. The ratio of effective connectivity was calculated. The effect of treatments on the DMN connectivity was explored with a  $2 \times 3$  repeated measure ANOVA with the three original treatment groups and visits as factors. The connectivity changes between the responder and non-responder groups were assessed using a  $2 \times 2$  repeated measure ANOVA with groups and visits as factors.

All statistical analyses involving connectivity were adjusted with the LEDD and performed directly on CONN. Data of significant clusters were then exported in jamovi (version 2.3.28) to perform the post-hoc tests with Bonferroni corrections for multiple comparisons.

**Data and code availability.** The data discussed in this article are still being processed for their clinical significance and are not the exclusive property of our lab. They can only therefore be made available upon request with a data sharing agreement and following publication of the main OXYDOPA paper.

### 3. Results

Among the 45 PD patients with central pain that might have been included in this neuroimaging study, only 38 were analysed. A total of 7 patients dropped out: 2 in the placebo group (n = 1 patient withdrawal and n = 1 adverse effect); 1 in the levodopa group (n = 1 prohibited concomitant medication); and 4 in the oxycodone group (n = 4 adverse

effects). **Table 1** reports the demographic and clinical data of these patients. No statistical differences were found between the three groups of patients at baseline.

In all patients, we witnessed a decrease in the mean and maximal VAS scores over time ( $-14.9 \pm 18$ ,  $p < 0.001$ ;  $-17.3 \pm 12$ ,  $p < 0.001$ ) without identifying any significant differences between the 3 treatment groups ( $-20.1 \pm 16.1$  in placebo,  $-8.3 \pm 12.6$  in levodopa, and  $-16.2 \pm 25.6$  in oxycodone).

#### 3.1. Relationship between pain and resting-state connectivity in seed-to-voxel analyses at baseline

The mean VAS scores were negatively correlated to connectivity measures between the right anterior insula ( $r = -0.624$ ) and a cluster covering a part of the posterior cingulate gyrus (PCC) (cluster 1) at baseline.

The mean VAS scores were also negatively correlated to connectivity measures between the left accumbens and two clusters covering a part of brainstem ( $r = -0.718$ ) (cluster 2) and a part of the right hippocampus ( $r = -0.743$ ) (cluster 3) at baseline.

The clusters and the correlations are presented in **Figs. 1 and 2**, respectively. Our statistics are summarized in **Table 2**.

#### 3.2. Effects of the treatments on resting-state connectivity

We observed no statistical difference regarding resting-state connectivity between the three groups of treatment for the three analysed seeds before treatment.

There was no interaction between the two factors (groups of treatment and visits) affecting the connectivity of the three analysed seeds and for the mean and maximal VAS.

#### 3.3. Changes of connectivity among the responder and non-responder groups

Due to a discrepancy between the mean VAS score and the interview (which revealed that the patient had experienced an improvement in pain intensity after treatment, whereas the percentage change in mean VAS showed a worsening of this pain after 8 weeks, meaning that the mean VAS was incorrectly assessed for this patient), one patient was excluded.

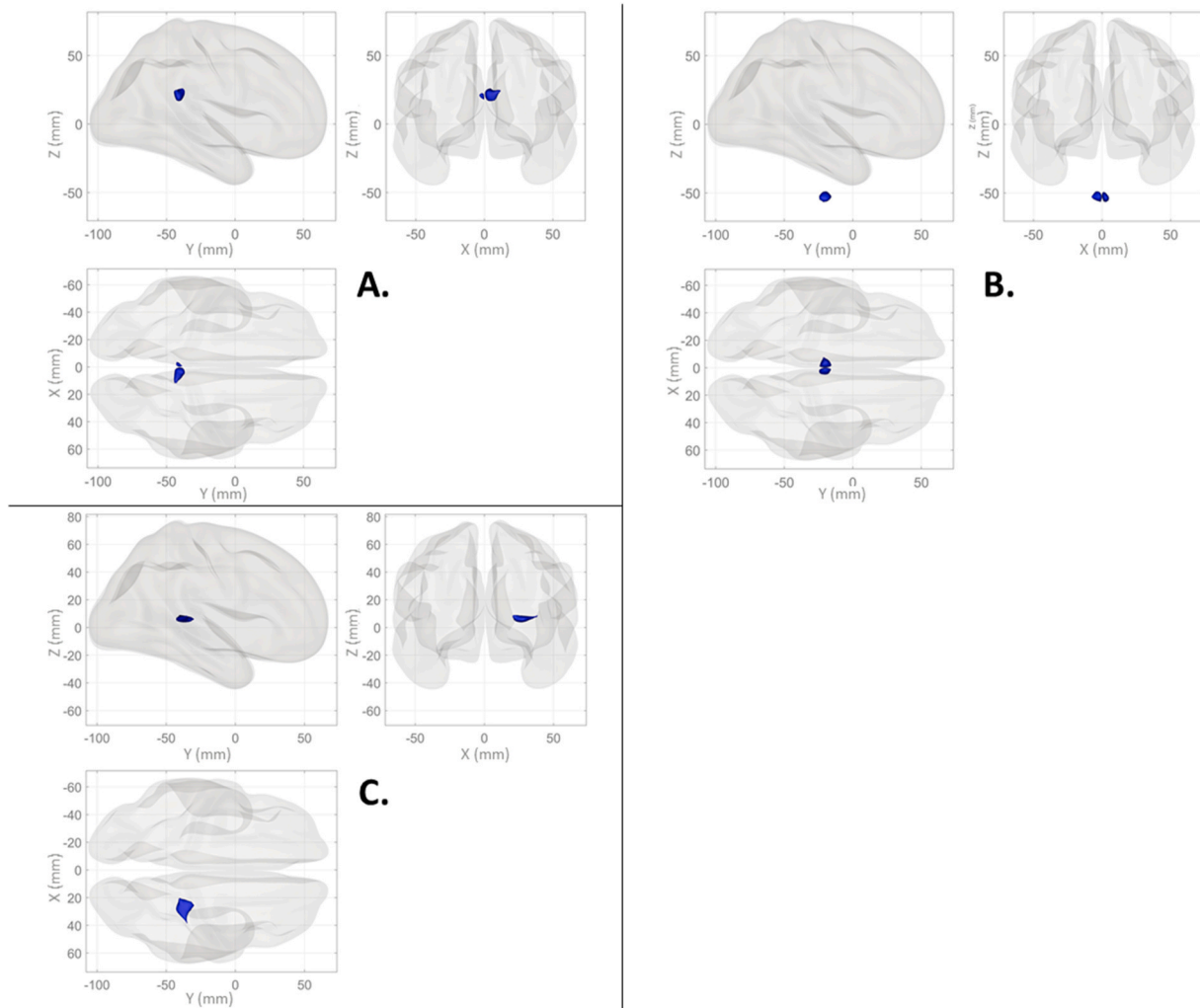
In all patients, the median change of VAS scores after treatment was  $-16.7\%$ . All PD patients with a decrease of VAS greater than  $16.7\%$

**Table 1**  
Demographic and clinical data at baseline.

	Population	Placebo	Levodopa	Oxycodone	Difference between groups p-value
N	38	13	14	11	
Age	64.6 ± 7	67.3 ± 6.06	64.6 ± 5.66	61.2 ± 8.51	0.15
Disease duration	6.82 ± 3.43	7.29 ± 3.52	7.69 ± 4.03	5.18 ± 1.94	0.07
Sex (female)	15	6	5	4	0.94
LEDD (mg/d)	1162 ± 659	1479 ± 726	1073 ± 603	864 ± 487	0.05
MDS-UPDRS III	21.1 ± 9.19	17.1 ± 5.97	21.3 ± 10.5	25.9 ± 9.26	0.06
Mean VAS	58.3 ± 17.7	57.9 ± 19.8	54.8 ± 20.9	63 ± 9.1	0.39
Maximal VAS	79.9 ± 14.4	75.9 ± 14.1	80.1 ± 16.5	85 ± 11.5	0.23
MPQ	20.8 ± 8.04	18.6 ± 7.59	21.9 ± 10.2	22.2 ± 5.38	0.38
KPPS	41.8 ± 19.6	42.4 ± 24.1	45.9 ± 19.3	36.1 ± 12.5	0.32
BPI	33 ± 11	34.9 ± 11.3	30.4 ± 9.42	33.8 ± 12.8	0.52
HAD	17.7 ± 6.15	16.6 ± 5.72	18.6 ± 7.16	18 ± 5.74	0.66
-HAD-A	10.1 ± 3.6	9.5 ± 3.03	10.5 ± 3.82	10.2 ± 4.21	0.73
-HAD-D	7.66 ± 3.64	7.07 ± 3.54	8.08 ± 4.07	7.91 ± 3.48	0.72
PDQ-39	33.4 ± 10.5	31.6 ± 10.3	30.7 ± 11.5	38.5 ± 8.36	0.12
FSS	4.68 ± 1.62	4.48 ± 1.33	4.68 ± 1.88	4.92 ± 1.73	0.60
PSQI	10 ± 3.5	10.3 ± 2.79	8.85 ± 3.98	11.1 ± 3.67	0.38

Means ± standard deviations; LEDD: levodopa equivalent daily dose; MDS-UPDRS III: Movement Disorder Society – Unified Parkinson's Disease Rating Scale part III; VAS: Visual Analogue Scale; MPQ: McGill Pain Questionnaire; KPPS: King's Parkinson Pain Scale; BPI: Brief Pain Inventory; HAD: Hospital Anxiety and Depression; PDQ-39: Parkinson's Disease Questionnaire 39 items; FSS: Fatigue Severity Scale; PSQI: Pittsburgh Sleep Quality Index. For all variables, there was no statistical difference between groups  $p > 0.05$ .





**Fig. 1. Representation of the significant clusters in right lateral, posterior, and superior views. A.** Cluster 1 (+08–40 + 22) has a size of 145 voxels and is covering 86 voxels covering 4 % of the posterior division of the cingulate gyrus and 59 voxels covering a non-labelled area around the cingulate gyrus. **B.** Cluster 2 (+00–18 -54) has a size of 148 voxels covering less than 1 % of the brainstem. **C.** Cluster 3 (+28–40 + 06) has a size of 144 voxels and is covering 11 voxels covering 2 % of the right hippocampus and 133 voxels covering an unlabelled area next to it.

were classified as responders ( $n = 18$ ), while the others were classified as non-responders ( $n = 19$ ). There was no significant difference in demographic and clinical variables between the two groups at baseline (Appendices - Table 1). There were 6 responders in the levodopa group, 4 in the oxycodone group, and 8 in the placebo group.

At baseline, we observed no difference between the two groups (responders vs. non-responders) with regard to connectivity. In both groups, we witnessed a change in connectivity over time between the right anterior insula and a cluster of 428 voxels covering a part of the PCC (cluster 4, MNI: +12–38 + 26, size  $p$ -FDR = 0.000083, size  $p$ -unc = 0.000003, Fig. 3A). Indeed, the responders showed a significant decrease in connectivity (responders connectivity at baseline =  $0.090 \pm 0.096$ ; after treatment =  $-0.052 \pm 0.118$  and difference =  $-0.142 \pm 0.130$ ;  $p < 0.001$ ) while the non-responders showed a significant increase (non-responders connectivity at baseline =  $0.003 \pm 0.119$ ; after treatment =  $0.092 \pm 0.133$  and difference =  $0.089 \pm 0.130$ ;  $p = 0.012$ ) (Fig. 3B).

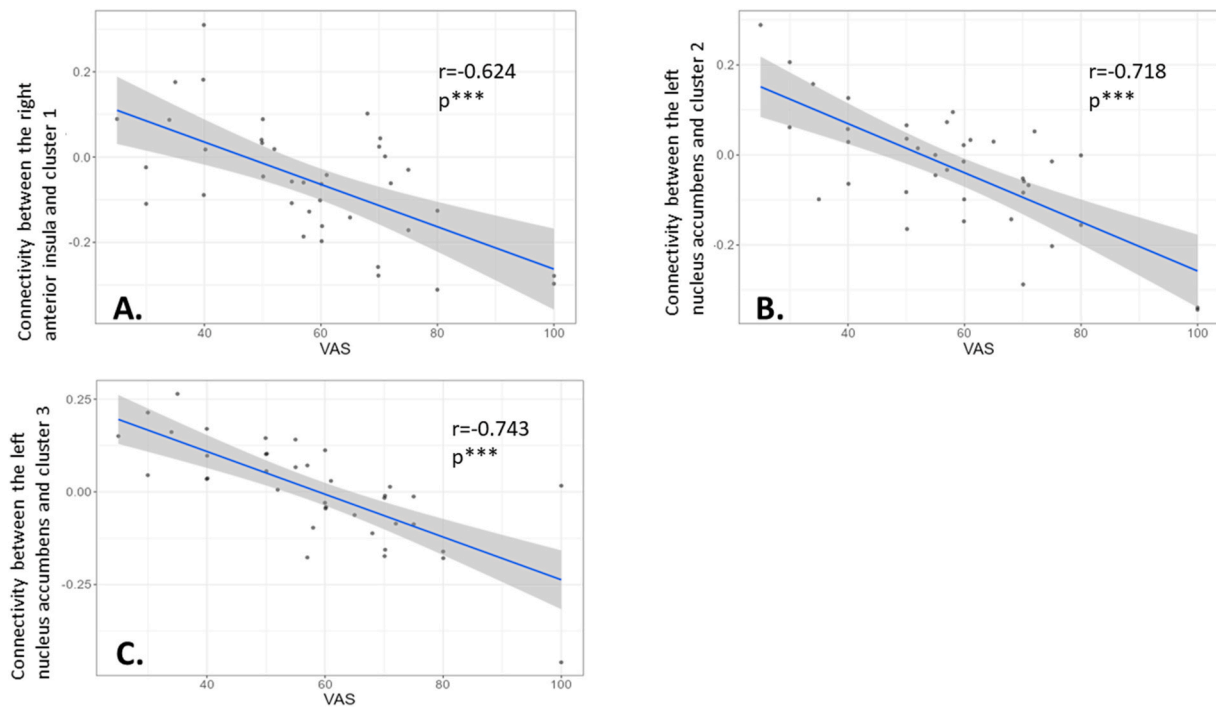
These changes in connectivity were correlated with the decrease of the mean and maximal VAS scores ( $\rho = 0.787$ ,  $p < 0.001$ ;  $\rho =$ ,  $p < 0.001$ , respectively). There was no significant correlation between connectivity and any other changes in pain questionnaires or clinical parameters (motor, psychological, etc.).

### 3.4. ROI-to-ROI analyses in the DMN

All the areas of the DMN formed a network with a ratio of connectivity of 52 % before treatment. There was no correlation between the VAS scores and the connectivity of the DMN. There was no specific change in connectivity within the DMN after treatment in the three groups of treatment. There was no specific change in connectivity within the DMN in the responder and non-responder groups after dividing the patients into further groups according to their pain reduction.

## 4. Discussion

In PD patients with central pain, pain intensity was negatively correlated with the connectivity between the right anterior insula and the PCC, and between the left accumbens and two clusters: part of the brainstem and the right hippocampus. The higher the pain level, the lower the connectivity between these regions. Levodopa and oxycodone treatments did not induce specific change in connectivity but there was a decrease in connectivity in the responders regardless of treatment, as opposed to an increase in the non-responders between the right anterior insula and the left PCC.



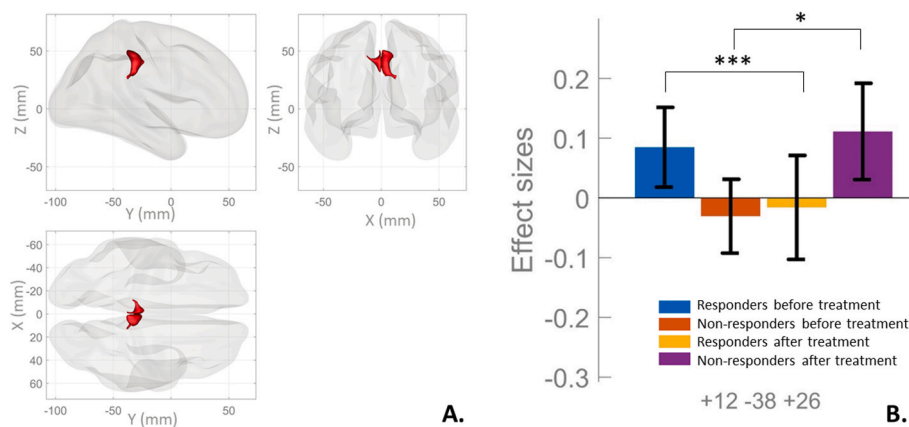
**Fig. 2. Correlations between mean VAS and connectivity at baseline.** A. Correlation between mean VAS and the connectivity between the right anterior insula and cluster 1. B. Correlation between mean VAS and the connectivity between the nucleus accumbens and cluster 2. C. Correlation between mean VAS and the connectivity between the nucleus accumbens and cluster 3. The correlation analyses were performed in CONN. Data of significant clusters were exported and Pearson correlations were obtained using the VAS scores before treatment.  $p^{***} = p < 0.001$ .

**Table 2**

Descriptions and statistics of functional connectivity (seed and target) correlated to VAS scores at baseline.

Seeds	Clusters	Coordinates	Size (voxels)	Size p-FDR	Size p-unc	R	correlation p-value
Right anterior insula	Cluster 1 ( <i>part of the cingulate gyrus</i> )	+08-40 + 22	145	0.046049 <sup>a</sup>	0.004186	-0.624	$p < 0.001$
Left nucleus accumbens	Cluster 2 ( <i>part of the brainstem</i> )	+00-18 -54	148	0.033352 <sup>a</sup>	0.003543	-0.718	$p < 0.001$
Left nucleus accumbens	Cluster 3 ( <i>part of the right hippocampus</i> )	+28-40 + 06	144	0.033352 <sup>a</sup>	0.003924	-0.743	$p < 0.001$

<sup>a</sup> p-FDR-corrected  $< 0.05$ .



**Fig. 3. Changes in connectivity between responders and non-responders, before and after treatments.** A. Representation of cluster 4: Cluster 4 (+12-38 + 26) has a size of 428 voxels and is composed of 308 voxels covering 13 % of the posterior division of the cingulate gyrus, 29 voxels covering 7 % of the precuneus cortex, and 21 voxels covering less than 1 % of the left precentral gyrus. B. Representation of the changes in connectivity (median and quartiles) between the right anterior insula and cluster 4 adjusted with the LEDD. There was no significant difference in baseline between responder and non-responder groups.  $***p < 0.001$ ,  $*p < 0.05$ .

**4.1. Pain and brain connectivity at baseline**

The connectivity between the insula and the PCC could be implicated in the consciousness of pain. Indeed, the recruitment of the insula and

the PCC could enable the transition from a pre-conscious state of painful stimulation to full pain awareness (García-Larrea and Bastuji, 2018). Moreover, the insula is part of the Saliency Network (SN) and the PCC is part of the DMN, and both networks, which are related to the pain

experience, are disorganized in multiple chronic pain populations (Alshelhi et al., 2018; Kucyi and Davis, 2015). When a stimulus is perceived, the DMN, which is activated at rest, deactivates while the SN activates (Yeshurun et al., 2021). The PCC participates in the disengagement of the attentional focus (Leech and Sharp, 2014). An alteration in the interaction between these two networks could therefore lead to a diminished ability to disengage one's attention from pain, thus leading to the experience of chronic pain. Thus, the anti-correlated connectivity between the anterior insula and the PCC (negative connectivity) associated with higher pain in PD patients could represent an overactivation of the awareness of chronic pain.

During nociceptive stimulus, the ascendant pain signal to the brain areas can be modified by a descending pain system in the brainstem (Crawford et al., 2022). In our study, the connectivity between the nucleus accumbens and the brainstem that correlated with pain intensity could be considered as a dysregulation of this descending pain system, leading to a loss of pain control and a state of chronic pain in our PD patients. In patients at higher risk of lower back pain chronification, the accumbens shows both a decreased volume and changes in its functional connectivity (Makary et al., 2020). The brainstem is composed of the periaqueductal grey (PAG), the rostroventral medulla (RVM), and the ventral tegmental area (VTA). The PAG's connectivity was disrupted in patients suffering from chronic lower back pain. The connectivity with the RVM may be involved in the transition from acute to chronic pain (Heinricher, 2016) and the VTA undergoes a loss in its activation of the expectation of pain relief in chronic pain patients (Loggia et al., 2014; Yang et al., 2020). Therefore, that PD patients with higher pain intensity have low levels of connectivity between the accumbens and the brainstem could reflect the alteration of descending pain modulation.

The hippocampus has an important role in integrating sensory, autonomic, and affective information, in memory processes that involve context (Johnston and Amaral, 2004), and in the consolidation of pain perception in the memory, enabling subjects to develop behaviours designed to avoid pain (Garcia-Larrea and Bastuji, 2018; Ziv et al., 2010). The connectivity between the accumbens and the hippocampus could represent a hyper-consolidation of pain perception in our PD patients with chronic pain. Indeed, structural, molecular, and functional changes in the hippocampus in chronic pain patients could be involved in both learning and chronification of pain (Liu et al., 2018; Mansour et al., 2014; Mutso et al., 2012; Noorani et al., 2022; Soleimannejad et al., 2006). Furthermore, in PD patients with pain, functional connectivity between the hippocampus and some pain-related areas (accumbens and insula) was disrupted (Polli et al., 2016). This is consistent with our results, which identify a negative correlation between pain intensity and functional connectivity between the accumbens and the hippocampus.

Given that the insula is related to the awareness of pain, the PCC to self-consciousness, the accumbens to the development of pain avoidance behaviours, the hippocampus to learning and the processing of memory, and the brainstem to the pain descending system, it is reasonable to deduce that patients suffering from chronic pain related to PD have undergone a distortion of their memory and learning system, leading to a state of chronic pain.

#### 4.2. Brain connectivity and pain response

There was no specific change in connectivity after levodopa and oxycodone treatments compared to placebo, despite the involvement of dopamine and opioid receptors in pain management and analgesia (Borsook et al., 2010; Chudler and Dong, 1995; Serafini et al., 2020). This could be explained by the lack of a specific effect of these two drugs on pain reduction or by the high heterogeneity of connectivity values between subjects in our dataset, highlighted by the low functional connectivity ratio of the DMN at baseline.

The functional connectivity between the right anterior insula and the left PCC changed in opposite ways in the responder and non-responder

groups. Responders showed a decrease in connectivity while non-responders had increased connectivity. These changes were specific to pain relief as they were not correlated with any other clinical parameters such as psychological or motor states. As neither drug (oxycodone and levodopa) induced a reduction in pain in the responders, we suggest that the decrease in connectivity may be related to a placebo effect.

The placebo effect is a biological and symbolic phenomenon resulting from the administration of an inert substance accompanied by suggestions of clinical benefit (Price et al., 2008). In placebo analgesia, expectations (positive or negative) and learning are both implicated. Positive expectations lead to decreased anxiety and the activation of reward mechanisms, while learning is essential to behavioural conditioning and social learning. Imaging studies conducted during a nociceptive stimulation have identified brain regions involved in the expectation and inhibition of pain, such as the ACC, prefrontal cortex, accumbens, anterior insula, and PCC (Amanzio et al., 2011). By and large, the PCC is implicated in the transfer of the placebo effect from pain to emotional relief and the reduction of attention toward an unpleasant stimulus (Zhang and Luo, 2009). In our study, the decrease of connectivity between the anterior insula and the PCC in the responder group could be associated with decreased pain awareness, memories of previous pain relief experiences, and attention to pain (Barbiani and Benedetti, 2020).

One limit of the study is that sex was not used as an adjustment variable, since adding more co-variables would have decreased the statistical power of the analyses in our limited number of patients. Nonetheless, the sex ratio was not significantly different between the groups, meaning that any impact it might have had on our analyses would be very limited.

Moreover, the study design was originally built for a randomised controlled trial, aimed at exploring the effects of levodopa and oxycodone on central pain in PD patients. This initial study did not include a group of patients without pain, although such a group would have constituted an interesting control group for our exploratory study. Furthermore, due to the small sample size of this exploratory imaging study, comparing the connectivity of responders and non-responders within each treatment group was not possible because of a lack of statistical power.

## 5. Conclusion

To conclude, we have demonstrated that there is a link between the intensity of PD central pain and the connectivity of the anterior insula and nucleus accumbens. This could be due to a dysregulation of the learning and mesolimbic systems leading to a state of chronic pain, despite oxycodone and levodopa not showing any specific connectivity modification.

By contrast, the change in connectivity between the anterior insula and the PCC in responder patients could be associated with a decrease in pain awareness through the placebo effect.

To build further on our findings, we would need to investigate all the biopsychosocial factors involved in the variabilities between individuals' responses to treatments, and, in particular, to the responses to the placebo, in the management of chronic pain.

## Funding source

This study is a PHRC (Programme Hospitalier de Recherche Clinique, n° 14-0044) funded by the French Ministry of Health. The sponsor played no role in the conception, design, methodology, of the study, data analysis, or the preparation of this paper.

## Data/code availability statement

The data discussed in this article are still being processed for their clinical significance and are not the exclusive property of our lab. They



can only therefore be made available upon request with a data sharing agreement and following publication of the main OXYDOPA paper.

## Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Informed consent was obtained from all subjects involved in the study.

## CRediT authorship contribution statement

**Karel Joineau:** Writing – original draft, Formal analysis. **Mathilde Boussac:** Writing – review & editing, Supervision. **Patrice Peran:** Supervision. **David Devos:** Investigation. **Jean Luc Houeto:** Investigation. **Sophie Drapier:** Investigation. **David Maltete:** Investigation. **Jesus Aguilar:** Investigation. **Estelle Harroch:** Writing – review & editing, Project administration. **Margherita Fabbri:** Writing – review & editing, Investigation. **Clémence Leung:** Investigation. **Fabienne Ory-Magne:** Writing – review & editing, Investigation. **Melissa Tir:** Investigation. **Christine Tranchant:** Investigation. **Hayet Salhi:** Investigation. **Solène Frismand:** Investigation. **Frederique Fluchere:** Investigation. **Ana Marques:** Writing – review & editing, Investigation. **Olivier Rascol:** Investigation, Conceptualization. **Emeline Descamps:** Writing – review & editing, Supervision. **Christine Brefel-Courbon:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

## Data availability

Data will be made available on request.

## Acknowledgments

We would like to thank the following University Hospitals for patient data and MRI acquisition: Amiens, Clermont-Ferrand, Henri Mondor-Crétéil, Lille, Marseille, Nancy, Nantes, Poitiers, Rennes, Rouen, Strasbourg, and Toulouse. The authors would also like to thank the patients who participated in the study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ynirp.2024.100197>.

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