

**Functional imaging of deep brain stimulation
in Parkinson's disease :
from motor to non motor symptoms**

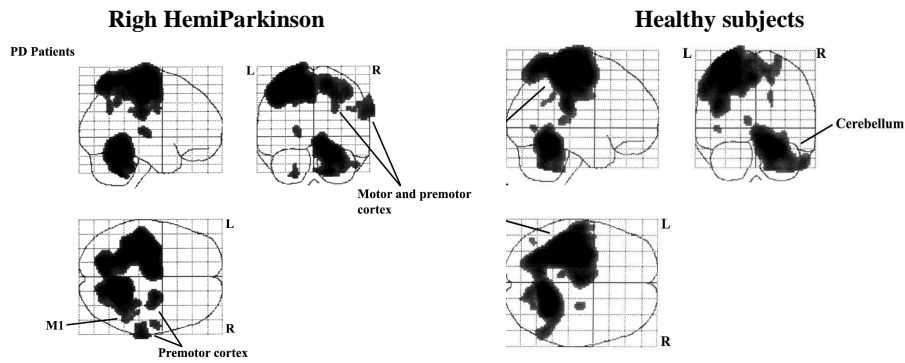
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Université Lyon I; Hôpital Neurologique Pierre
Wertheimer; CNRS, Centre de Neurosciences
Cognitives, Lyon, France

**Abnormalities of brain activation
in Parkinson's disease**

Accessory motor circuits are recruited in early-stage PD

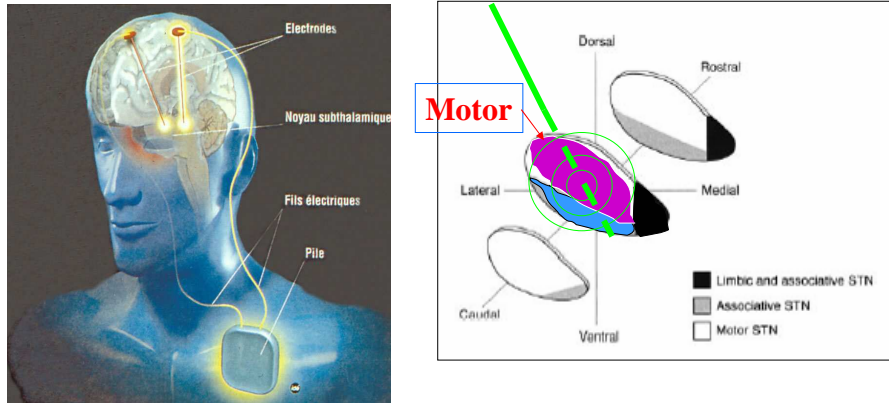
Motor task performed with the right / akinetic hand



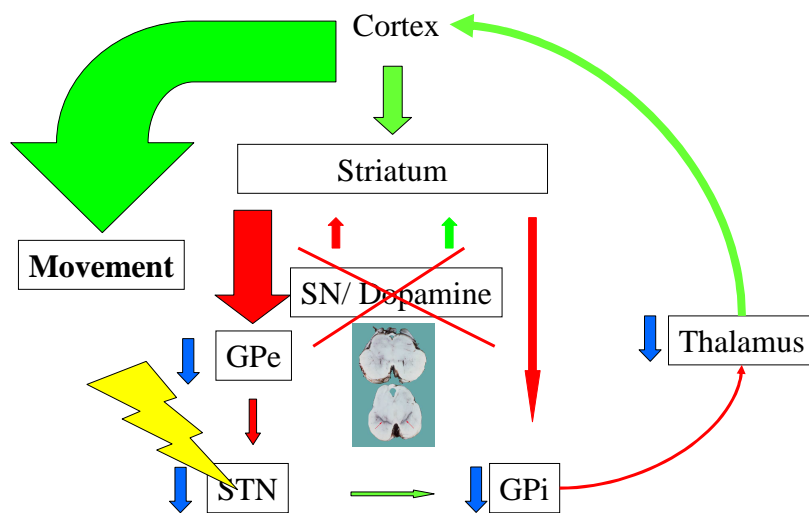
Thobois et al, Neuroreport. 2000

How DBS changes brain activation during motor performance in PD

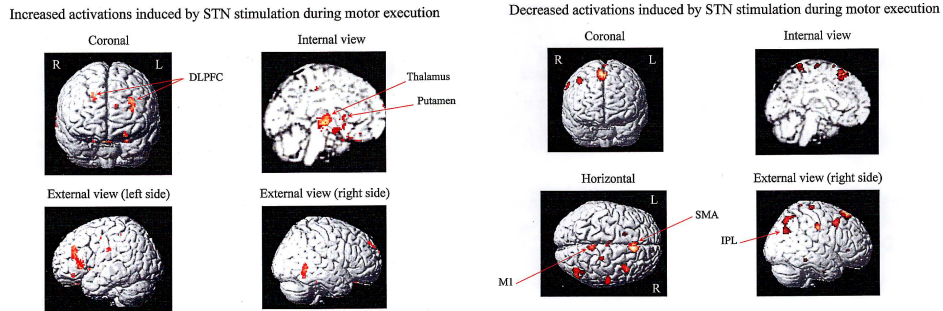
STN DBS and motor function in PD



Mechanism of action of STN DBS according to the model



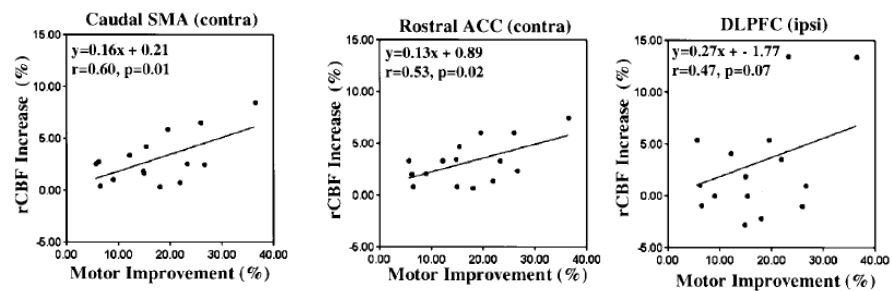
Consequences of STN stimulation during motor execution



- Restoration of cortical deactivations
- Suppression of accessory motor pathway recruitment

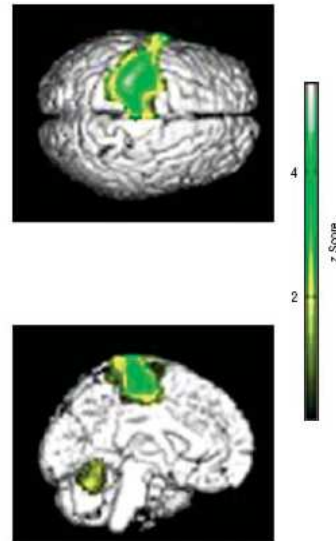
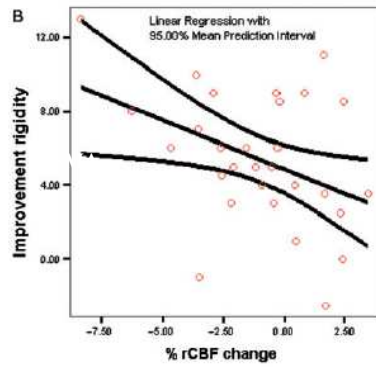
Thobois et al, J Neurol. 2002

The improvement of motor function is proportional to the increase of rCBF



Strafella et al, 2003 ; Karimi et al, 2008

Increased activation of deafferented cortical areas or suppression of a global brain overflow ?

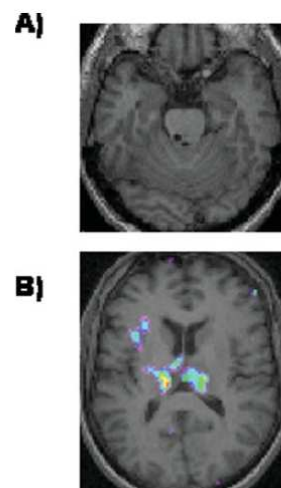
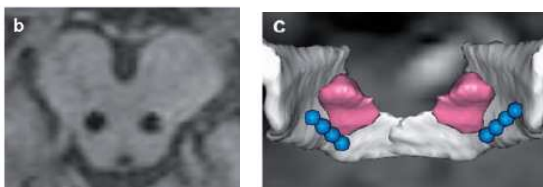


Payoux et al, 2004 ; Karimi et al, 2008

PPN DBS and gait disorders in PD

Effects of pedunclopontine nucleus area stimulation on gait disorders in Parkinson's disease

M. U. Ferraye,^{1,2} B. Debû,^{1,2} V. Fraix,^{1,2} L. Goetz,^{1,2} C. Ardouin,³ J. Yelnik,^{4,5,6} C. Henry-Lagrange,^{1,2} E. Seigneuret,³ B. Piallat,^{1,2} P. Krack,^{1,2,3} J.-F. Le Bas,^{1,2,3} A.-L. Benabid,^{1,2,3} S. Chabardès^{1,2,3} and P. Pollak^{1,2,3}



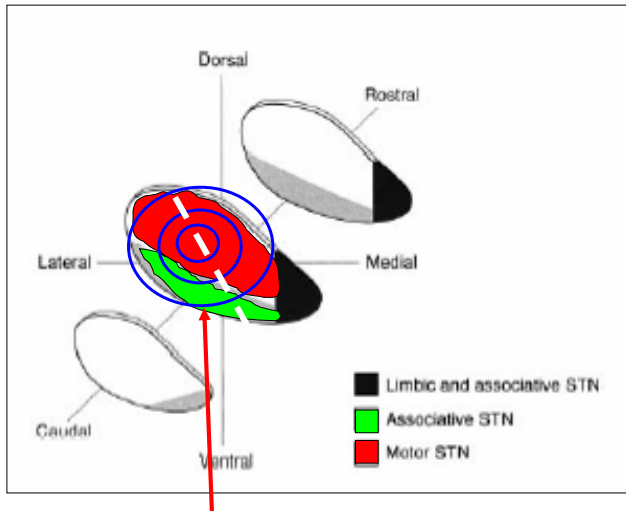
Stefani et al, 2007; Strafella et al, 2008; Ballanger et al, 2009; Ferraye et al, 2009

Synthesis on the motor effects of STN DBS

- STN DBS has major effects on motor symptoms in PD
- Consequences are task-dependent in terms of activation pattern
- Overall, STN DBS tends to normalize the cortical activation by :
 - ⇒ Increasing reduced cortical activity
 - ⇒ Restoring the selectivity of brain activation

How DBS changes brain activation during a cognitive task in PD

STN stimulation influences associative circuits



Some executive functions may be affected by the stimulation

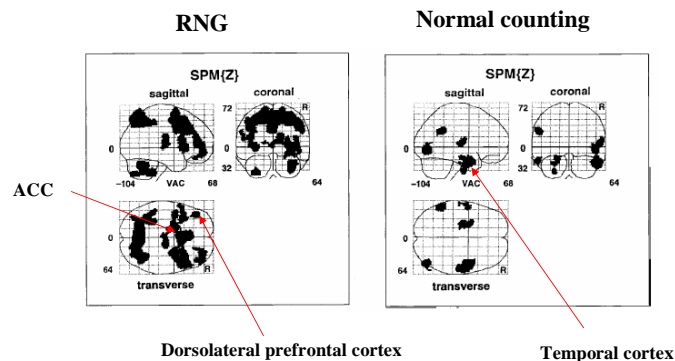
- Go-No-Go
- Stroop
- Verbal fluency

Associative

Ardouin et al, 1999 ;Jahanshahi et al, 2000; Pillon et al, 2000

Random number generation task

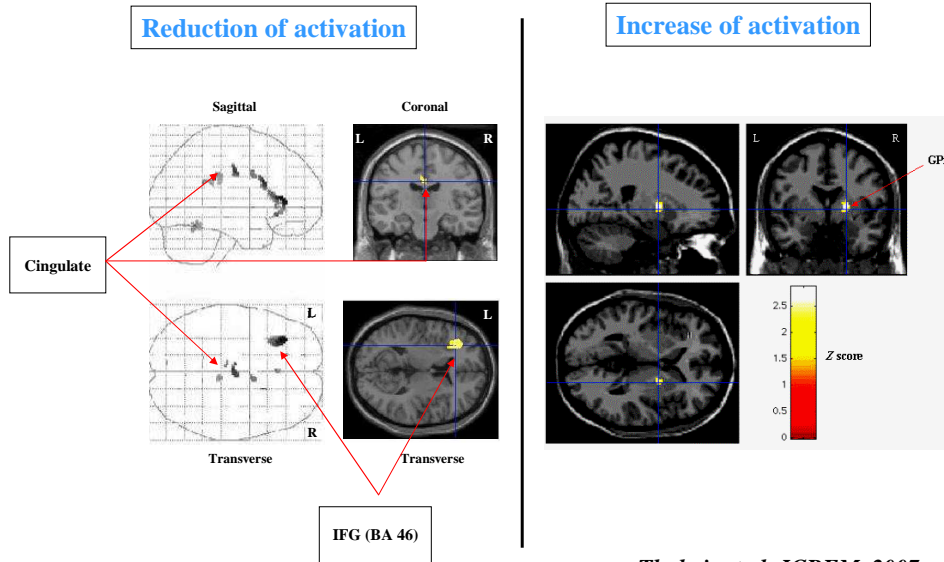
Healthy subjects



=> During RNG : activation of a PF-ACC network that inhibits the temporal cortex

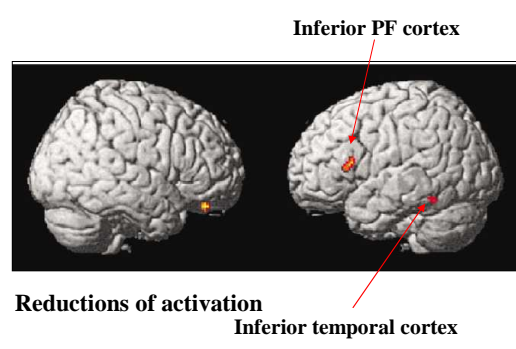
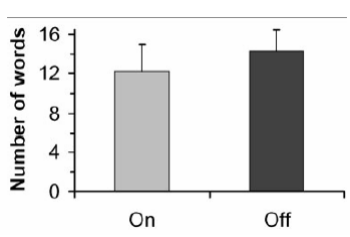
Jahanshahi et al, Neuroimage. 2000

Effect of STN stimulation during RNG

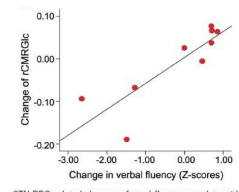


Effect of STN DBS on verbal fluency

STN stimulation reduces categorial verbal fluency



BA 44/45

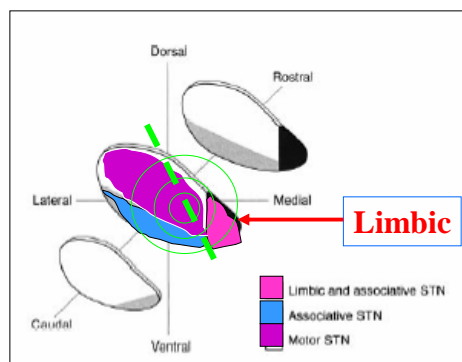


STN-DBS-related changes of word fluency correlate with alterations of cerebral metabolic rates of glucose in the left DLPFC (BA 46) ($r = 0.90, p = 0.0001, A$) and in the left Broca area (BA 44/45) ($r = 0.85, p = 0.004, B$).

Schroeder et al, 2003 ; Kalbe et al, 2009

STN stimulation, mood and behavior...

STN stimulation influences limbic circuits



Mirthful Laughter Induced by Subthalamic Nucleus Stimulation

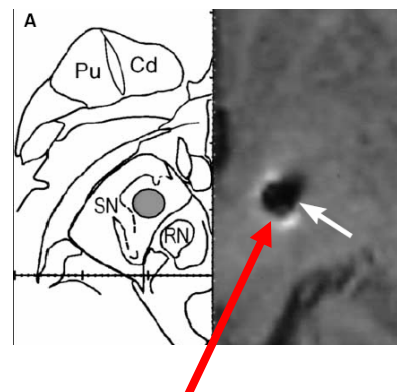
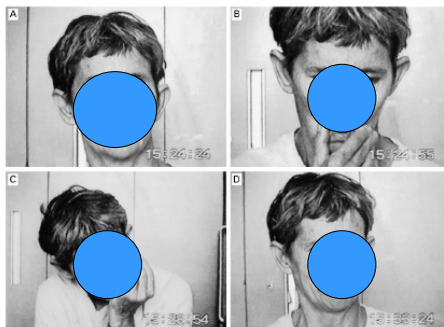
Paul Krack, MD,^{1,2*} Rajeev Kumar, MD,³ Claire Ardouin, PhD,¹ Patricia Limousin Dowsey, MD, PhD,^{1,4}
John M. McVicker, MD,³ Alim-Louis Benabid, MD, PhD,¹ and Pierre Pollak, MD¹



Krack et al, 2001

TRANSIENT ACUTE DEPRESSION INDUCED BY HIGH-FREQUENCY DEEP-BRAIN STIMULATION

BOULOS-PAUL BEJJANI, M.D.,
PHILIPPE DAMIER, M.D., PH.D., ISABELLE ARNULF, M.D.,
LIONEL THIVARD, M.D., ANNE-MARIE BONNET, M.D.,
DIDIER DORMONT, M.D., PHILIPPE CORNU, M.D.,
BERNARD PIDOUX, M.D., PH.D., YVES SAMSON, M.D.,
AND YVES AGID, M.D., PH.D.



Role of the substantia nigra ?

Bejjani et al, 1999

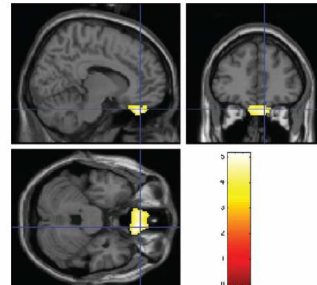
Subthalamic nucleus stimulation affects orbitofrontal cortex in facial emotion recognition: a pet study

F. Le Jeune,^{1,2,*} J. Péron,^{2,3,*} I. Biseul,³ S. Fournier,^{2,3} P. Sauleau,^{2,4} S. Drapier,^{2,3} C. Haegelen,^{2,5} D. Drapier,^{2,6} B. Millet,^{2,6} E. Garin,¹ J.-Y. Herry,¹ C.-H. Malbert⁷ and M. Vérin^{2,3}

Table 4 Percentage of correct RFE (mean \pm SD) before (preoperative condition, M-3) and after (postoperative condition, M+3) STN DBS in Parkinson's disease patients, and HC participants

	Preoperative condition (baseline) Mean \pm SD (%)	Postoperative condition (M+3) Mean \pm SD (%)	HC group Mean \pm SD (%)
Happiness	97.6 \pm 5.9	95.1 \pm 6.8	95 \pm 8.2
Sadness	64.2 \pm 25.1	59.6 \pm 25	55.6 \pm 24.6
Fear	54.1 \pm 22.2	38.1 \pm 31.9 [#]	51.3 \pm 22.9
Surprise	95.9 \pm 24	87.9 \pm 19.2	89 \pm 18.6
Disgust	94.6 \pm 7	87.4 \pm 14.8	89 \pm 11.7
Anger	67 \pm 25.7	58 \pm 25.9	67.5 \pm 25.4
No emotion	80.2 \pm 24.4	81.3 \pm 24.3	85.7 \pm 19.4
Total score	83.6 \pm 21.6	75.6 \pm 10.3 ^{##}	76.1 \pm 11.4

[#] $p < 0.05$ and ^{##} $p < 0.01$ when compared with preoperative condition (Wilcoxon's test for paired samples).



Role of the OFC in facial emotions recognition (Adolphs et al, 2002).

Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior

Luc Mallet^{*††}, Michael Schüpbach[†], Karim N'Diaye[§], Philippe Remy[¶], Eric Bardinet[§], Virginie Czernecki^{||}, Marie-Laure Welter[†], Antoine Pelissolo^{**}, Merle Ruberg^{††}, Yves Agid^{†,††}, and Jérôme Yelnik^{††}

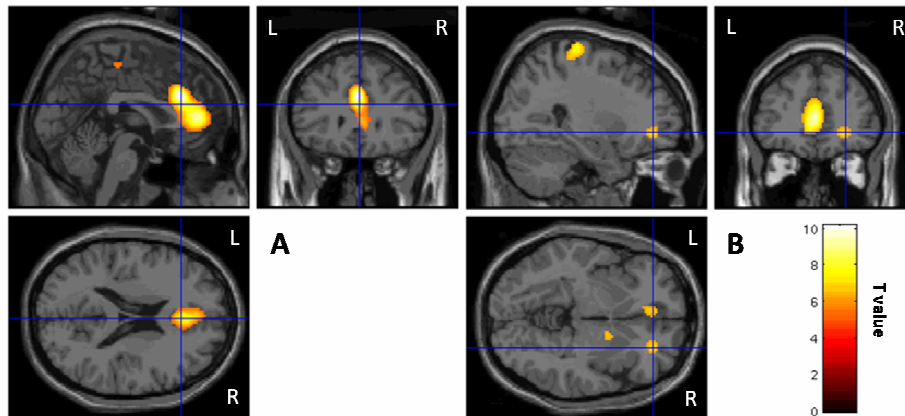
PNAS | June 19, 2007 | vol. 104 | no. 25 | 10661–10666

Manic behaviour induced by deep-brain stimulation in Parkinson's disease: evidence of substantia nigra implication?

M Ulla, S Thobois, J-J Lemaire, A Schmitt, P Derost, E Broussolle, P-M Llorca, F Durif

J Neural Neurosurg Psychiatry 2006;77:1363–1366. doi: 10.1136/jnnp.2006.096628

Increase of brain activation during DBS induced mania



Ulla, Thobois et al, submitted

Post-operative apathy

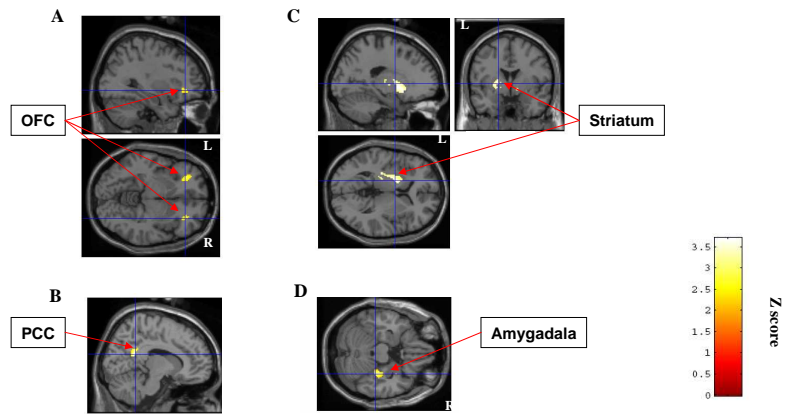


Prevalence of apathy after surgery

- ✓ 8.7 % before surgery
- ✓ 24.6 % at 3 years post-op
- ✓ 17 % at 5 years postop

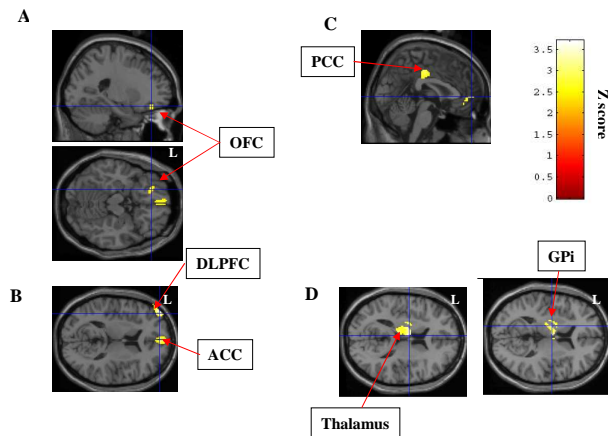
Funkiewiez et al, 2004 ; Krack et al, 2003; Voon et al, 2006

Apathetic patients have more pronounced reduced endogenous dopamine level than non apathetic patients in limbic areas



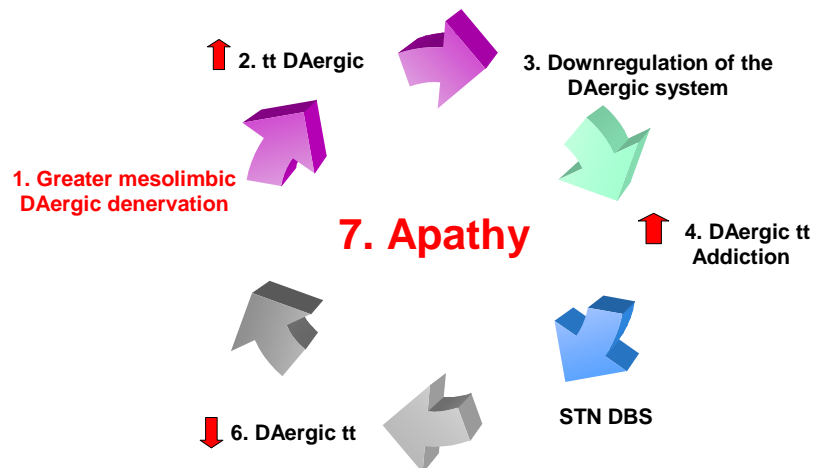
Thobois et al, Brain, 2010

After methylphenidate, non apathetic patients release a greater amount of dopamine than apathetic patients in limbic areas



Thobois et al, Brain, 2010

Toward a mechanism of apathy after STN DBS in PD?



Conclusion

- DBS represents a unique tool to modulate in vivo basal ganglia circuitry
- Functional imaging is mandatory to better assess the consequences (expected or not) and mechanism of action of DBS
- The development of **new targets** for **new indications** will benefit from functional imaging studies for both the understanding of the underlying disease and of the mechanism of action of DBS (G de la Tourette, depression, OCD...)

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- ✓ M. Ulla
- ✓ PM Llorca

CNRS, UMR 52-29

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- ✓ B. Ballanger

Grenoble

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- ✓ C. Ardouin, E. Lhommée
- ✓ V. Fraix
- ✓ A. Benabid, S. Chabardes

London

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- ✓ P. Limousin
- ✓ M. Hariz
- ✓ G. Hotton, D. Brooks

Aix-en-Provence

- ✓ S. Pinto