

# PHYSIOPATHOLOGIE EN NEUROLOGIE ET PSYCHIATRIE

**Jeudi 6 Decembre**

Durée total de l'examen : 2 heures

Vous devez répondre à deux sujets aux choix parmi les trois sujets proposés. Si vous choisissez le sujet 3, PENSEZ à remettre le sujet (page 5) avec le schéma annoté dans votre copie, après y avoir indiqué votre NOM.

Total examination duration: 2 hours

You must respond to two exams topics from the three proposed. If you choose topic n° 3, REMEMBER to include the examination paper (page 5) in your copy, after having indicating your name on both.

## PREFRONTAL CORTICES AND ACTION MONITORING

**P. Burbaud**

**Sujet / Topic 1 ----- Page 1**

Durée du sujet : 1 heure

Dégagez les propriétés fonctionnelles essentielles des trois grandes régions du cortex préfrontal (dorsolatéral, orbital et cingulaire) en vous appuyant sur les données de la clinique et de l'expérimentation.

Test duration: 1 hour

Explain the functional properties of the three main regions of the prefrontal cortex (dorsolateral, orbital and cingulate) using clinical and experimental data.

# NEUROIMAGING IN NEUROLOGICAL DISEASES

M. Bonnet

Sujet / Topic 2 ----- pages 2 to 4

Durée du sujet : 1 heure

L'examen est une analyse d'une partie d'un article portant sur l'utilisation de la technique d'IRMf lors de sollicitations cognitives chez des patients au premier évènement clinique évocateur de la Sclérose en Plaques (stade CIS).

Vous avez à votre disposition, sur deux feuilles consécutives, une partie de la Méthode et des Résultats.

D'après votre cours :

- interprétez les résultats obtenus par l'équipe de recherche
- étayez votre propos en apportant des comparaisons avec les résultats obtenus en NeuroImagerie dans la SEP, dans d'autres pathologies neurodégénératives et chez le sujet sain
- pourquoi l'imagerie fonctionnelle se justifiait-elle dans cette étude ?
- en quoi les résultats de cette étude peuvent être utiles pour la prise en charge des patients ?

Test duration: 1 hour

You have to review a part of an article focused on the use of the fMRI technique during cognitive demands in Clinically Isolated Syndrome (CIS) patients (first clinical episode of Multiple Sclerosis disease).

Truncated Methods and Results sections are provided on two separate pages.

According to the lecture:

- interpret the results obtained by the authors
- bring comparisons with neuroimaging results obtained in MS, in others neurodegenerative diseases and in healthy context.
- explain the relevance of the fMRI technique in this study
- in what way these results could be useful for MS patients?

## Subjects and methods

### Subjects

A group of patients with CIS fulfilling, at inclusion, at least the dissemination in space criteria of McDonald (dissemination in space established by magnetic resonance imaging (MRI), or positive cerebrospinal fluid plus two or more MRI-detected lesions consistent with MS [19]) were tested. These patients underwent fMRI exploration at the beginning of the study (+3 months after their first acute clinical attack; M0) and again one year later (M12). Among the initial population of 18 CIS patients [5], only 13 patients (72%) were tested one year later: four of the original group of patients had moved away from Marseille for professional reasons, and the data on one patient had to be removed because of head movements occurring during the scanning procedure. None of the patients stopped the follow-up process because of MS-related problems.

Nineteen control subjects matched in terms of age, sex, and educational level were also tested at a single time-point using the same fMRI procedures. These healthy control subjects were included in the study to provide standard baseline activation profiles. The study then focused on the changes in the patterns of activation observed in the patients, which were correlated with their PASAT performances to determine whether the regional patterns of activation recorded were linked to the cognitive performances. Based on the changes in the PASAT scores between M0 and M12, the patients were divided into two groups. Group A included subjects whose PASAT scores improved and group B included subjects whose scores worsened or remained the same.

Subjects' functional deficits were assessed using the Expanded Disability Status Scale (EDSS) [20] and the multiple sclerosis functional composite (MSFC) score [21,22] (the PASAT scores used to compute the MSFC were recorded in the scanner during fMRI). All subjects (patients and controls) were right-handed (>70% Oldfield scale) [23], native French speakers and naive with respect to the PASAT test at the first sitting. They gave their informed consent to participate in this experiment, which was approved by the local Ethics Committee (Timone Hospital, Marseille, France).

## Results

### Clinical characteristics

The clinical and demographic characteristics of patients and control subjects are given in Table 1. MS had been diagnosed based on McDonald's criteria in all the patients in whom comparisons were made between the MRI carried out at M0 and M12.

Mean PASAT score recorded during fMRI in the whole group of patients was 38 (SD = 12) at M0 and 43 (SD = 9) at M12. Mean PASAT score obtained by the control subjects was 48 (SD = 8) at the single time point (M0).

Post-hoc classification of patients into two groups was performed at M12, depending on whether their PASAT scores at M12 were below, above, or exactly the same as the M0 scores. PASAT scores at M12 increased in eight patients (group A) (PASAT<sub>M0</sub> = 33 (SD = 12), PASAT<sub>M12</sub> = 44 (SD = 9)) and remained unchanged ( $n = 1$ ) or decreased ( $n = 4$ ) in five patients (group B) (PASAT<sub>M0</sub> = 45 (SD = 10), PASAT<sub>M12</sub> = 41 (SD = 10)). At M12, two patients in group A and two patients in group B fulfilled the Poser criteria for MS [26].

No differences in age, sex, educational level, MSFC score, or T<sub>2</sub> lesion load were found to exist between these two groups of patients.

For information : the Paced Auditory Serial Addition Task (PASAT). This task involves speed and working memory processes, as well as addressing some aspects of executive functions, calculation, and arithmetic fact retrieval [5].

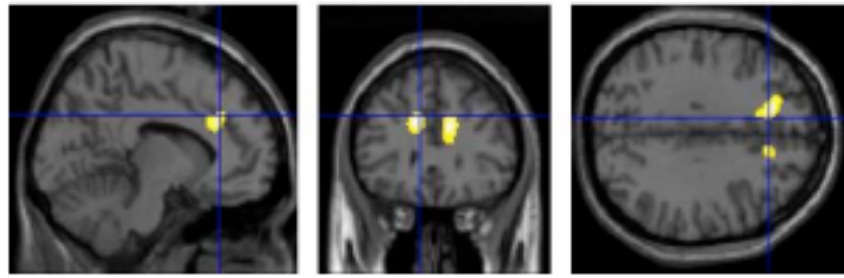
**Table 1** Demographics and clinical characteristics of patients and controls at M0 and M12

	All patients (n = 13)		Group A: MS patients showing increased PASAT scores between M0 and M12 (n = 8)		Group B: MS patients showing reduced (n = 4) or unchanged (n = 1) PASAT scores between M0 and M12		Controls (n = 19)
	M0	M12	M0	M12	M0	M12	
Age, mean (SD)	29.46 (6.00)		30.75 (6.76)		27.40 (4.45)		25.79 (5.99)
Sex (M/F)	4/9		2/6		2/3		4/17
Educational level in years, mean	14		13.6		14.7		14
Mean duration since the presenting symptom in months, mean (SD)	5.85 (2.12)		5.00 (1.60)		7.20 (2.28)		
EDSS, median (range)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–1.5)	1 (0–1.5)	1 (0–2)	
MSFC, mean (SD)	-0.343 (0.96)	0.032 (0.69)	-0.618 (0.87)	0.065 (0.66) <sup>b</sup>	0.097 (1.02)	-0.022 (0.81)	-0.175 (0.60)
PASAT, mean (SD)	38.15 (12.36) <sup>a</sup>	43.00 (8.71)	33.88 (12.11) <sup>a</sup>	44.38 (8.56) <sup>b</sup>	45.00 (10.32)	40.80 (9.47)	48.00 (7.97)
Percentage of changes in the PASAT scores between M0 and M12, mean (SD)		+15% (9)		10.5% (6.4)		-4.2% (3.3)	
T <sub>2</sub> lesion load, mean (SD), cm <sup>3</sup>	1.92 (1.67)	2.15 (1.85)	2.37 (1.99)	2.31 (1.80)	1.19 (0.60)	1.88 (2.11)	

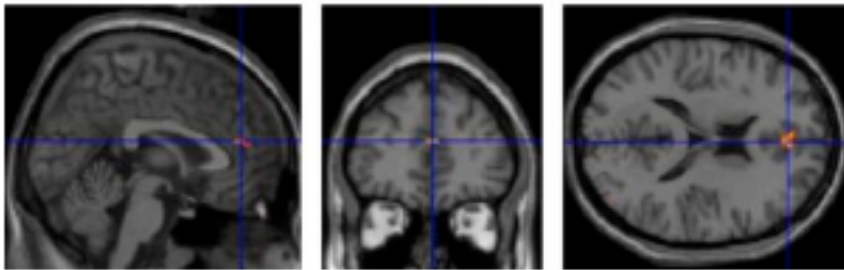
MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Task; EDSS, Expanded Disability Status Scale; MSFC, multiple sclerosis functional composite

<sup>a</sup>Significant difference relative to group of controls (Mann-Whitney test).

<sup>b</sup>Significant difference relative to M0 in the same group (Wilcoxon test).



**Figure 1** Increase in cortical activation during PASAT at M0 observed in patients with normal and subnormal PASAT performances (mean score of controls  $\pm$  1.5 standard deviation) ( $n = 6$ ) relative to controls. Significant changes are located in the anterior cingulate cortex (BA 24/32) and the right lateral prefrontal cortex (BA 46), and the bilateral thalami (two sample t-test,  $p = 0.001$  corrected for extent threshold).



**Figure 2** Decrease in cortical activation during PASAT at M12 relative to baseline (M0) observed in group B patients ( $n = 5$ ). Significant decreased activation is located inside the anterior cingulate cortex (paired t-test,  $p = 0.001$  corrected for extent threshold).

Group B: MS patients showing decreased ( $n = 4$ ) or unchanged ( $n = 1$ ) PASAT scores between M0 and M12.



**Figure 3** Increase in cortical activation during PASAT at M12 observed in group A patients ( $n = 8$ ) relative to group B patients ( $n = 5$ ). Significant changes are located in the anterior cingulate cortex (BA 24/32) and the right lateral prefrontal cortex (BA 45/46) (Random effect, two sample t-test,  $p = 0.001$  corrected for extent threshold).

Group A: MS patients showing increased PASAT scores between M0 and M12 ( $n = 8$ ).

Group B: MS patients showing decreased ( $n = 4$ ) or unchanged ( $n = 1$ ) PASAT scores between M0 and M12.

**Indiquez votre Nom :**

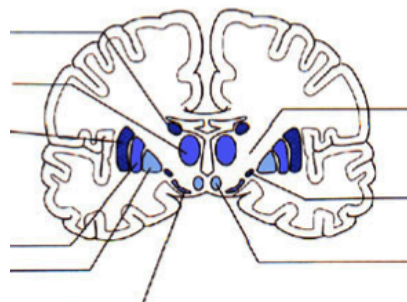
## **DE LA CLINIQUE A L'ANATOMIE FONCTIONNELLE DANS LES SYNDROMES PARKINSONIENS**

**D. Guehl**

**Sujet 3 ----- Pages 5 et 6**

Durée du sujet : 1 heure

1/ Vous décidez de vous lancer dans la compréhension du fonctionnement des ganglions de la base (GB) par une approche électro physiologique chez le primate sub-humain. Mais avant cela, vous devez être sûr de vos connaissances sur l'anatomie des GB. Légendez le schéma suivant qui représente une coupe coronale (frontale) de cerveau:

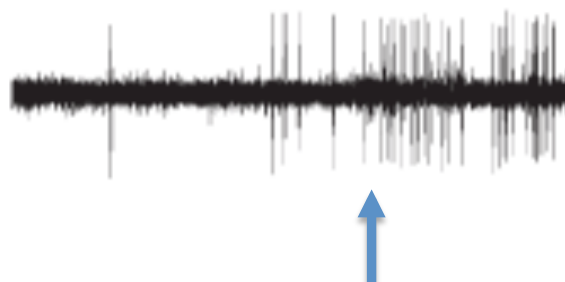


2/A l'aide de la technique d'enregistrement extra cellulaire unitaire, vous explorez les GB de l'hémisphère gauche d'un primate sub-humain et obtenez l'activité suivante (tracé brut d'enregistrement) au moment où il initie un mouvement avec sa patte droite (flèche) :



Vous concluez que la structure que vous êtes en train d'enregistrer est le pallidum interne (GPi). En utilisant vos connaissances sur l'organisation fonctionnelle des GB, expliquez pourquoi.

3/ Vous déplacez votre électrode et obtenez une autre activité (tracé brut d'enregistrement) qui vous laisse penser que vous avez changé de structure. Devant les caractéristiques de l'enregistrement unitaire suivant, quels sont les éléments qui vous orientent vers une activité du thalamus moteur ? (la flèche correspond toujours à l'initiation du mouvement avec la patte controlatérale aux enregistrements de l'activité neuronale)



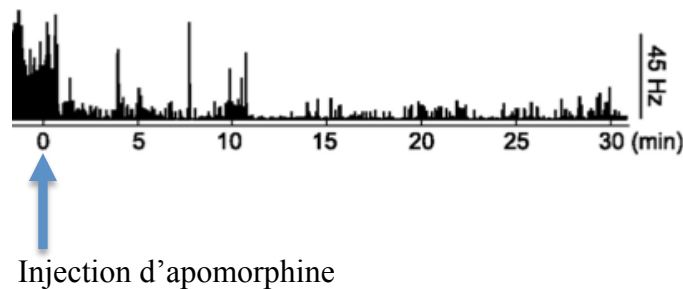
4/ En déplaçant votre électrode une fois de plus, vous rencontrez l'activité unitaire (tracé brut d'enregistrement) suivante alors que l'animal est au repos:



a/Vous apprenez que cet animal a reçu des injections de MPTP (un toxique de la chaîne respiratoire mitochondriale). Cette activité neuronale vous paraît-elle compatible avec une activité de noyau sous thalamique (NST) chez un singe ayant reçu du MPTP ? Expliquez pourquoi.

b/Le MPTP est surtout utilisé pour modéliser une maladie neurodégénérative. Laquelle ?

5/Chez cet animal intoxiqué au MPTP, vous décidez d'étudier les effets d'un agoniste dopaminergique D2 puissant (apomorphine injectée par voie systémique) sur l'activité neuronale du NST. Dans les cinq minutes qui suivent l'injection apomorphine vous constatez l'apparition de mouvements anormaux involontaires au niveau des pattes de l'hémicorps droit de votre animal.



a/Commentez les effets de l'apomorphine visible sur l'activité neuronale (histogramme de fréquence) ci-dessus.

b/ Quels sont les mécanismes qui expliquent ces modifications d'activité du NST ?

c/A quoi correspondent les mouvements anormaux involontaires que vous observez ? En vous basant sur vos connaissances de l'organisation fonctionnelle des GB et sur l'enregistrement ci-dessus, comment pouvez vous expliquer la survenue de tels mouvements ?

d/ Si vous deviez détruire une structure des GB pour supprimer ces mouvements anormaux involontaires, laquelle choisiriez-vous ? Pourquoi ?

Remember to put your Name :

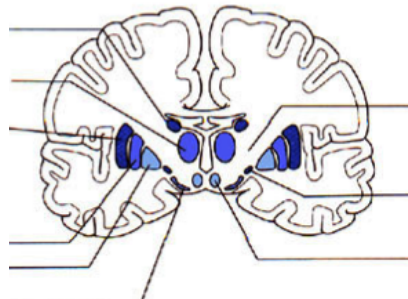
## FROM CLINIQUE TO FUNCTIONAL ANATOMY OF EXTRA-PYRAMIDAL SYNDROMS

D. Guehl

Topic 3 ----- pages 5 and 6

Test duration: 1 hour

1/ You wish to understand the functioning of the basal ganglia (BG) using an electrophysiological approach in subhuman primates. But beforehand, you must ensure how accurate is your knowledge of the BG anatomy. Label the following diagram that represents a coronal (frontal) view of a human brain:

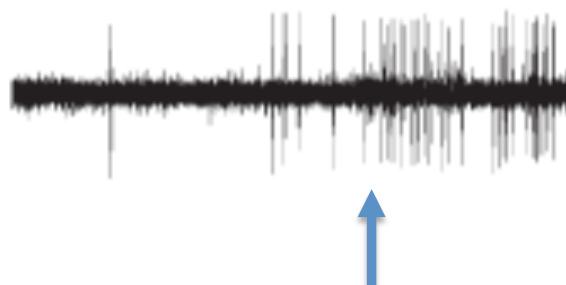


2/ Here is the raw electrophysiological trace of a recorded neuron before and after a subhuman primate initiated a movement with his right paw (arrow):



Using your knowledge of the functional organization of BG, explain why you could conclude that the recorded structure is the internal pallidum (GPi).

3/ You move your electrode and record a new single unit activity suggesting that you move to another structure. Regarding the pattern of the neuronal activity, what are the details that suggest you may have recorded a motor thalamic activity? (arrow = movement initiation)



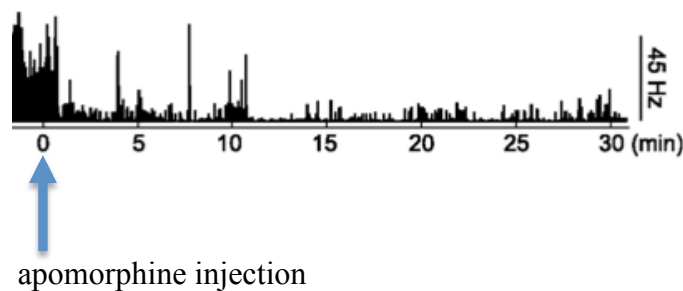
4/ By moving your electrode again, you find the following electrophysiological single unit activity while the animal is at rest:



a/ Knowing that the animal has previously received injections of MPTP (a mitochondrial toxin of respiratory chain), do you think that this neuronal activity is compatible with a subthalamic activity in a MPTP intoxicated monkey? Justify.

b/ MPTP is mainly used to model a neurodegenerative disease. Which one ?

5/ In this MPTP intoxicated monkey, you decide to investigate the effects of a D2 dopamine agonist (apomorphine; systemic injection) on STN neuronal activity. Within five minutes after apomorphine injection, you saw the appearances of abnormal involuntary movements in the right arm and leg.



a/ Describe and comment the effects of apomorphine on the above peri-event frequency histogram.

b / What are the mechanisms explaining these STN's neuronal changes ?

c / What are the abnormal involuntary movements you observe? Based on your knowledge of the functional organization of BG and the peri-event frequency histogram just above, how can you explain the occurrence of such movements?

d / You decide to remove a structure of BG to suppress these abnormal involuntary movements. What would be your choice? Why?