

# **PHYSIOPATHOLOGIE EN NEUROLOGIE ET PSYCHIATRIE**

**Mardi 24 Novembre**

Durée total de l'examen : 2 heures

Vous devez répondre aux deux sujets. PENSEZ à indiquer votre numéro d'étudiant sur le feuillet de réponse (page 2).

Total examination duration: 2 hours

You must respond to the two exams topics. REMEMBER to indicate your student number on page 2 of this examination paper.

Numéro étudiant/  
Student number : \_ \_ \_ \_ \_

## MCQ exam (20 pts)

Test duration: 1 hour

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This exam contains 40 multiple choice questions, each worth 0.5 points.

Indicate with a cross the correct response(s) for each question. Each question could have several correct answers. Make sure that your answer is clearly marked.

## MCQ exam

Mark your answers on the answer sheet (page 2)

1. **In patients with major depressive disorder, abnormalities of the HPA axis include:**
  - a) increased levels of CRF in cerebrospinal fluid, as compared to normal healthy subjects.
  - b) decreased levels of ACTH in plasma, as compared to normal healthy subjects.
  - c) increased levels of cortisol in plasma, as compared to normal healthy subjects.
  - d) decreased levels of vasopressin in plasma, as compared to normal healthy subjects.
  - e) increased levels of free cortisol in urines, as compared to normal healthy subjects.
  
2. **The combined dexamethasone/CRF test causes:**
  - a) a more pronounced elevation of plasma cortisol levels in depressed patients, as compared to normal healthy subjects.
  - b) a less marked elevation of plasma cortisol levels in depressed patients, as compared to normal healthy subjects.
  - c) a less marked reduction in plasma CRF levels in depressed patients, as compared to normal healthy subjects.
  - d) a more pronounced elevation of plasma cortisol levels in the first-degree relatives of depressed patients, as compared to the first-degree relatives of normal healthy subjects.
  - e) a less marked elevation of plasma cortisol levels in the first-degree relatives of depressed patients, as compared to the first-degree relatives of normal healthy subjects.
  
3. **In the laboratory animal models, overexpression of MR (“mineralocorticoid receptors”) in forebrain causes:**
  - a) a reduction in the corticosterone response to stress.
  - b) a reduction in the anxiety levels.
  - c) a reduction in the 5HT1A receptor density in the hippocampus.
  - d) a reduction in the GR (“glucocorticoid receptors”) density in the hippocampus.
  - e) a reduction in the 5HT2A receptor density in the amygdala.
  
4. **In patients with obsessive-compulsive disorder (OCD), functional abnormalities within the frontal-subcortical loops include in resting conditions:**
  - a) a reduction in the metabolic activity within the anterior cingulate cortex, as compared to normal healthy subjects.
  - b) a reduction in the metabolic activity within the caudate nucleus, as compared to normal healthy subjects.
  - c) an increase in the metabolic activity within the orbitofrontal cortex, as compared to normal healthy subjects.
  - d) an increase in the metabolic activity within the thalamus, as compared to normal healthy subjects.
  - e) a reduction in the metabolic activity within the hippocampus, as compared to normal healthy subjects.

- 5. In the flanker-interference task, the magnitude of the so-called ERN (“error-related negativity”) is:**
- a) reduced in OCD patients, as compared to normal healthy subjects.
  - b) reduced in the first-degree relatives of OCD patients, as compared to the first-degree relatives of normal healthy subjects.
  - c) increased in OCD patients, as compared to normal healthy subjects.
  - d) increased in the first-degree relatives of OCD patients, as compared to the first-degree relatives of normal healthy subjects.
  - e) increased in OCD patients regardless of the level of clinical improvement in response to standard treatments.
- 6. In the first-degree relatives of OCD patients, cognitive and behavioral malfunctions were observed, including:**
- a) impaired cognitive flexibility.
  - b) impaired motor inhibition.
  - c) impaired error detection.
  - d) impaired action planning.
  - e) impaired episodic memory.
- 7. Autism is a pervasive developmental disorder which appears:**
- a) after 6 years old.
  - b) after 9 years old.
  - c) after 7 years old.
  - d) after 10 years old.
  - e) during early childhood.
- 8. Autism diagnosis is based on:**
- a) imaging data.
  - b) genetic data.
  - c) metabolomic data.
  - d) blood data.
  - e) clinical examination.
- 9. Autism can be associated to:**
- a) genetic diseases.
  - b) epilepsy.
  - c) motor disorder.
  - d) language disorder.
  - e) hyperactive and attentional deficit disorder.
- 10. In Autism:**
- a) social cognition is preserved.
  - b) sensori-perception can be altered.
  - c) eye-tracking studies can be used to measure gaze orientation.
  - d) eye-tracking studies can be used to measure pupil dilatation.
  - e) cortical ERP have evidenced atypical auditory cortical activation.

**11. In Autism**

- a) Psychotropic drugs are used to cure autism.
- b) Social rehabilitation programs are proposed to young children.
- c) The effectiveness of therapies is based on brain plasticity.
- d) 20 % of patients have very positive outcomes.
- e) Pharmacological drugs can be used to treat emotional dysregulation disorders.

**12. In Autism**

- a) Hyporeactivity to vocal sounds is observed.
- b) Lack of eye contact is one of the earliest signs.
- c) 1 000 genes may be involved.
- d) Abnormal brain cytoarchitecture is observed on MRI.
- e) Brain overgrowth is observed in the first two years of life in some cases.

**13. Multiple sclerosis is a disease :**

- a) with a subacute course.
- b) affecting the central nervous system.
- c) Inflammatory.
- d) inherited.
- e) affecting preferentially the elderly.

**14. Cognitive disturbances in multiple sclerosis :**

- a) could occur at all stages of the disease.
- b) increased the risk of unemployment.
- c) concern mainly language.
- d) are characterized by information processing speed impairment.
- e) spared executive functions.

**15. Cognitive impairment in multiple sclerosis:**

- a) cannot be detected by asking questions about cognition to the patient.
- b) can be detected in many patients by a single test assessing information processing speed.
- c) can be detected in many patients by a single test assessing episodic memory.
- d) can be assessed by the Mini Mental Status (MMS).
- e) is more severe in patients with a lower educational background than in more educated people with the same burden of disease lesions on MRI.

**16. Cognitive disturbances in multiple sclerosis :**

- a) correlate weakly with lesion load on MRI.
- b) correlate strongly with brain atrophy at the early stages of the disease on MRI.
- c) correlate with diffuse white matter involvement at early stages of the disease on MRI.
- d) do not correlate with MRI parameters in highly educated patients.
- e) correlate specifically with frontal lobe lesion load on MRI.

- 17. Brain activity during a cognitive task performed normally by a patient with multiple sclerosis:**
- a) is characterized by a decreased activity in the brain area associated with the task.
  - b) is associated with the same pattern of recruitment of brain areas than healthy subjects.
  - c) is characterized by recruitment of additional cerebral areas normally not involved in the task.
  - d) is dependant of the extent of diffuse brain tissue injury.
  - e) is limited in complex tasks.
- 18. The cerebellum**
- a) is involved in cognition in healthy subjects.
  - b) is functionally linked to the frontal lobe.
  - c) is activated during some automatic cognitive tasks in healthy subjects.
  - d) is activated during complex cognitive task in multiple sclerosis patients.
  - e) could be more activated after cognitive rehabilitation in multiple sclerosis patients.
- 19. What is the proportion of familial forms of Parkinson disease?**
- a) 100%
  - b) 90%
  - c) 50%
  - d) 20%
  - e) 10%
- 20. Despite the reduction in ATP production, what is the other consequence of impaired mitochondrial respiration?**
- a) Increased production of reactive oxygen species.
  - b) Increased of protein synthesis.
  - c) Mitochondria biogenesis.
  - d) Mitosis.
  - e) No other consequence.
- 21. Mitochondrial dysfunction in PD has been linked to Parkinson disease. What are the evidences?**
- a) Reduced complex I activity.
  - b) Increased production of mitochondrial-derived ROS.
  - c) ROS-mediated mtDNA damage.
  - d) Reduced complex I activity and increased production of mitochondrial-derived ROS.
  - e) Reduced complex I activity, Increased production of mitochondrial-derived ROS and ROS-mediated mtDNA damage.
- 22. What are the pathways converging into lysosomes?**
- a) Macroautophagy, chaperone-mediated autophagy, endocytosis, phagocytosis, microautophagy.
  - b) Macroautophagy, chaperone-mediated autophagy, endocytosis, phagocytosis.
  - c) Macroautophagy, chaperone-mediated autophagy, phagocytosis, microautophagy.
  - d) Macroautophagy, endocytosis, phagocytosis, microautophagy.
  - e) Macroautophagy and endocytosis.

- 23. Among the following propositions, select the correct item(s)**
- a) Rigidity observed in Parkinson's disease (PD) could be related to a degeneration of the pedunculopontine nucleus.
  - b) The striatum encompasses the internal part of the pallidum and the caudate nucleus.
  - c) The striatum contains only GABAergic medium spiny cells.
  - d) The thalamo-cortical pathway is glutamatergic.
  - e) The striatum inputs coming from the cerebral cortex are GABAergic.
- 24. Among the following propositions, select the correct item(s)**
- a) During Parkinson's disease (PD), neuronal activity of the subthalamic nucleus is decreased when the patient is off dopa (in the absence of levodopa intake).
  - b) During PD, neuronal activity of the internal part of the pallidum (GPi) is increased when the patient is off dopa.
  - c) During PD, neuronal activity of the thalamus is decreased when the patient is off dopa.
  - d) During PD, neuronal activity of the supplementary motor area (SMA) is decreased when the patient is off dopa.
  - e) During PD, neuronal activity of the GPi is increased when the patient is on dopa.
- 25. Among the following propositions, select the correct item(s)**
- a) The subthalamic nucleus (STN) receives inputs only from the external part of the pallidum (GPe).
  - b) Dopamine receptors D1 are present at the surface of the medium spiny neurons involved in the direct pathway.
  - c) STN neurons are cholinergic neurons.
  - d) Hyperactivity of the GPe can induce akinesia.
  - e) A lesion of the right STN can induce dyskinesia on the contralateral hemi-body.
- 26. An antidromic spike is characterized**
- a) It occurs at a fixed latency.
  - b) It occurs at a variable latency.
  - c) It follows high frequency stimulation.
  - d) It collides with spontaneously-occurring spikes.
  - e) It travels back to the soma from its initiation site.
- 27. Risks factors for PTSD**
- a) Blood cortisol levels.
  - b) Previous traumatic experience.
  - c) Hyperactivation of the amygdala.
  - d) Family history of PTSD.
  - e) History of drug abuse.
- 28. What are perineuronal nets**
- a) A subpopulation of excitatory neurons.
  - b) A highly organized form of proteoglycans.
  - c) A subpopulation of inhibitory neurons.
  - d) Glial cells.
  - e) Elements of the extracellular matrix.

**29. Principal therapies for PTSD**

- a) Cognitive and behavioral therapies.
- b) Hypnosis.
- c) Eye movement desensitization and reprogramming.
- d) Antidepressant/antipsychotic.
- e) Electroconvulsive shocks.

**30. Anatomy of the amygdala**

- a) The basolateral amygdala is a cortical-like structure.
- b) The central amygdala is a cortical-like structure.
- c) The central amygdala is a striatal-like structure.
- d) The basolateral amygdala is a striatal-like structure.
- e) The basolateral amygdala is composed of 80% of excitatory neurons.

**31. The plasma half-life of levodopa is**

- a) 15-30 min
- b) 1 – 1.5 h
- c) 3 – 5 h
- d) 5 – 8 h
- e) 10 – 15 h

**32. Rasagiline is**

- a) A selective dopamine D3 receptor antagonist.
- b) A reversible monoamine oxidase-B (MAO-B) inhibitor.
- c) A serotonin reuptake inhibitor.
- d) A reversible MAO-A and MAO-B inhibitor.
- e) An irreversible MAO-B inhibitor.

**33. Which of the following statements about monoamine oxidase (MAO) enzyme distribution is (are) false?**

- a) MAO-B are highly represented in the brain.
- b) MAO-A are highly represented in the brain.
- c) MAO-A are highly represented in the gastrointestinal tract.
- d) MAO-B are highly represented in blood platelets.
- e) MAO-A are present in the liver.

**34. Which of the following statements concerning the Catechol-O-methyltransferase (COMT) enzyme is (are) false?**

- a) COMT participate in the metabolism of levodopa and dopamine.
- b) COMT degrade dopamine into 3-O-methyldopa.
- c) COMT degrade levodopa into 3-O-methyldopa.
- d) 3-O-methyldopa facilitates the transfer of levodopa across the blood brain barrier.
- e) Selegiline is a selective COMT inhibitor.

**35. Which of the following statements is (are) false? In parkinsonian patients, the association of an COMT and levodopa:**

- a) Increases the bioavailability of the levodopa.
  - b) Increases the quality of life.
  - c) Reduces the fluctuations of plasma-levodopa levels.
  - d) Reduces motor fluctuations by increasing the “OFF” periods.
  - e) Provides a continuous dopamine-receptor stimulation.
- 

Clinical case:

Mr Y, 65 years old, is addressed for behavioral troubles which appeared after a stroke, 6 months ago. He exhibited a hemiplegia predominant in the left lower limb associated to ischemia on the CT scan. He had no speech disorder and partially recovered from his motor troubles. When he entered your office, his stand and gait were correct although he apparently had some weakness in his left leg. He is in a very good mood, which is surprising, and his jokes are a bit crude and inappropriate. When you asked questions, the answers are not always adapted ; apparently he has some attentional deficit. His wife report that his very poor minded now and forget everything as soon you tell him. He also has difficulty on training for new abilities.

**36. On the basis of these clinical symptoms, you evoke possible lesions of the (one or several exact answers) :**

- a) Primary motor cortex
- b) Dorsolateral prefrontal cortex
- c) Primary visual cortex
- d) Temporal cortex
- e) Orbitofrontal cortex

**37. Concerning the dorsolateral prefrontal cortex (CPFDL) (one or several exact answers) :**

- a) It encompass areas 8 and 46 in the Broadman classification.
- b) CPFDL neurons increase their activity during working memory processes.
- c) Working memory only concerns verbal information.
- d) All types of information processed in working memory involve the same region of the CPFDL.
- e) During working memory tasks the CPFDL, only, is recruited.

**38. Concerning the orbitofrontal cortex (one or several exact answers):**

- a) the orbitofrontal cortex (OFC) allows to filter non adapted information from the surrounding word.
- b) OFC lesions may induce troubles in social behavior.
- c) OFC dysfunctioning may lead to mental rigidity.
- d) There is a OFC dysfunctioning in obsessive-compulsive disorders.
- e) The OFC is involved in the evaluation of emotional consequences of action.

- 39. Concerning the anterior cingulate cortex (ACC) (one or several exact answers):**
- a) This region plays an important role in attentional processes.
  - b) It is involved in behavioral monitoring.
  - c) There is a dysfunctioning of this area in Tourette's syndrome.
  - d) ACC neurons are involved in visuo-motor processing.
  - e) The ACC is involved in working memory.
- 40. Finally, your patient seems to exhibit several troubles related to a dysfunctioning of the prefrontal cortex. Choose the good answers (one or several) :**
- a) Euphoria and unadapted behavior are due to ACC lesions.
  - b) Attention troubles are linked to ACC lesions.
  - c) Motor impairment in the lower limb is due to lesions of the motor and premotor cortices.
  - d) Troubles in working memory are related to a dysfunctioning of the CPFDL.
  - e) The whole clinical spectrum evokes a stroke in the vascular territory of the lateral cerebral artery.

# NEUROIMAGING IN NEUROLOGICAL DISEASES

M. BONNET

Test duration: 45 minutes (20 pts)

You have to review a part of an article focused on the use of the fMRI technique during memory task in Multiple Sclerosis patients.

According to the lecture:

- Interpret the results obtained by the authors
- Bring comparisons with other neuroimaging results obtained in MS using same/different tasks
- Bring comparisons with results obtained in other neurodegenerative diseases.
- Explain the relevance of the fMRI technique in this study and explain in what way these results could be useful for MS patients

**TABLE I. Demographic and clinical measures of healthy controls (HC), cognitively preserved (CP), and cognitively impaired (CI) MS patients**

	HC (n = 30)	CP (n = 34)	CI (n = 16)	P-value
Age (in years)	44.5 (8.8)	46.0 (9.2)	50.3 (5.6)	0.086
Sex (female/male)	19/11	27/7	8/8	0.051
Handedness (R/L/M)	26/3/1	32/2/0	13/3/0	0.449
Premorbid IQ	103.8 (10.8)	105.1 (12.3)	96.7 (12.4)	0.066
Educational level	5.7 (0.9)	5.8 (0.7)	5.2 (1.0)	0.401
Disease type (RRMS/ SPMS)	—	27/7	9/7	0.138
Disease duration (in years)	—	11.32 (6.6)	12.50 (7.3)	0.573
EDSS	—	4.1 (1.3)	4.3 (1.5)	0.404
HADS-A	3.0 (2.0–6.0)	5.0 (4.0–8.0)	6.5 (4.0–9.5)	<0.001 <sup>a</sup>
HADS-D	1.0 (0–2.3)	4.0 (2.5–6.3)	4.0 (3.0–5.8)	<0.01 <sup>a</sup>
CIS-20	25.0 (16.8–46.0)	72.5 (49.8–90.3)	80.5 (48.0–88.8)	<0.001 <sup>a</sup>

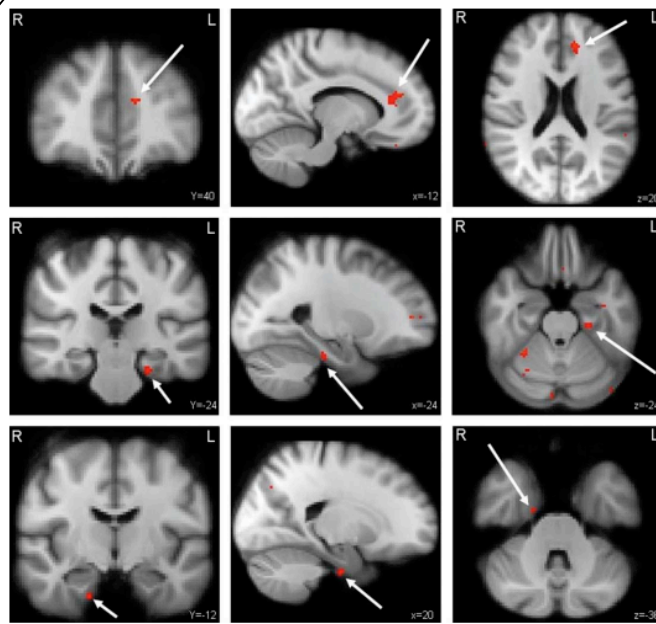
HADS: Hospital Anxiety and Depression Scale; A: anxiety; D: depression; CIS-20: Checklist individual strength, fatigue questionnaire. Data are means and (standard deviation) for normally distributed variables, variables EDSS, HADS-A, HADS-D, and CIS-20 were not normally distributed and therefore median (interquartile range) are provided.

<sup>a</sup>Significant differences were found between both patient groups and the healthy controls, the CP and CI patients did not differ significantly from each other.

## fMRI Paradigm

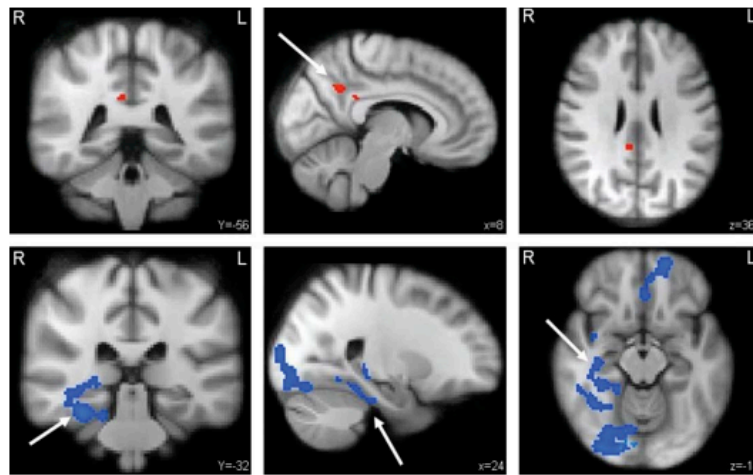
An episodic memory encoding paradigm [Van Der Werf et al., 2009] was used for fMRI measurements. This particular fMRI paradigm was chosen because of the reliable and robust activation of the hippocampus in healthy controls [Van Der Werf et al., 2009]. During the encoding phase, 50 different novel landscape images were presented to the subjects. Each picture was presented for 5 s in which the participants were asked to decide whether the images were “tropical” or “non-tropical” by pressing a button with either their left or their right index finger (Photon Control, Burnaby, BC, Canada). This ensures the encoding by requiring the subjects to attend to details in the images,

which has been shown to enhance hippocampal activation and subsequent recall [Daselaar et al., 2003]. The novel landscape images appeared in a pre-randomized order and were intermixed with 20 control images (a previously familiarized landscape image with a centrally positioned arrow pointing left or right, indicating which button to press). Thirty minutes following encoding, the retrieval phase was initiated. Here, a total of 100 landscape images were shown, 50 of which were novel and another 50 of which were old (i.e., already presented during the encoding phase), presented in a random order, intermixed with the same (arrow) control images. Participants had to indicate whether they had seen the pictures before, again by pressing the left or the right button. E-prime 1.1 software with service pack 3 (Psychology Software Tools, Pittsburgh) was used to present the images and to record all responses.



**Figure 1.**

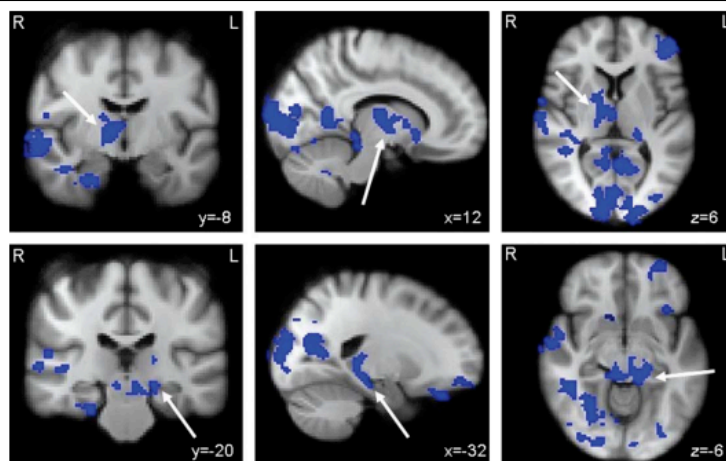
CP patients versus healthy controls. Differences in brain activation between CP patients and healthy controls during encoding of successfully recalled items. The areas in red were increased active in the CP patients. Upper panel: left anterior cingulate gyrus (arrow); Middle panel: left hippocampus (arrow) and parahippocampal area as well as cerebellar activation. Lower panel: right parahippocampal area (arrow) (Unclustered,  $Z \geq 3.1$ ,  $P \leq 0.001$ ).



**Figure 2.**

CI patients versus healthy controls. Differences in brain activation between CI patients and healthy controls during encoding of successfully recalled items. The areas in red display increased activation while the areas in blue display less activation in the CI patients. Upper row: activation in the precuneus (arrow) and

the posterior cingulate gyrus (unclustered,  $Z \geq 3.1$ ,  $P \leq 0.001$ ). Bottom row: extensive brain areas with less activation, the right hippocampus (arrow) and parahippocampal areas, right ventral visual stream and the left paracingulate gyrus extending into left frontal brain areas (cluster-corrected,  $Z \geq 2.3$ ,  $P \leq 0.05$ ).



**Figure 3.**

CI patients versus CP patients. Differences in brain activation between CI and CP patients during encoding of successfully recalled items. The areas in blue display less activation in the CI patients. Upper panel: brain regions with reduced activation were the left thalamus and right thalamus (arrow) as well as the ventral visual system, right superior and middle temporal gyrus,

frontal areas, cerebellum, and the right parahippocampal gyrus. Lower panel: less activation was found as well in the left hippocampus (arrow), right parahippocampal gyrus, the right nucleus accumbens, and areas within the brain stem (cluster-corrected,  $Z \geq 2.3$ ,  $P \leq 0.05$ )