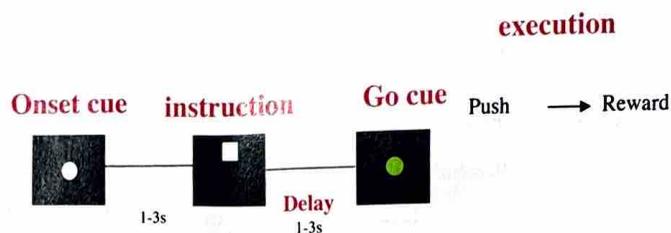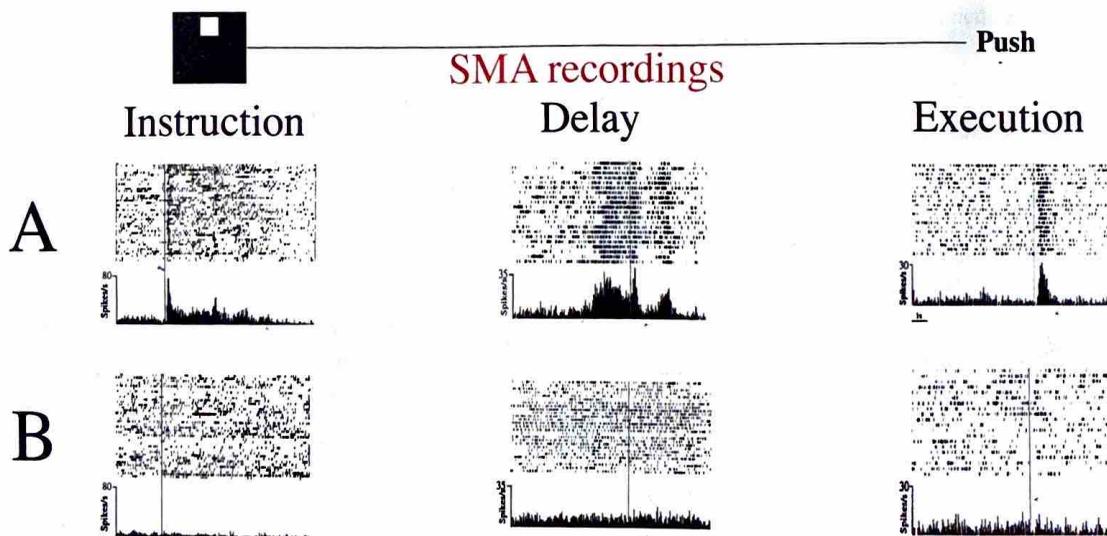**"From clinical to functional anatomy of extra-pyramidal syndroms"**

You have recorded single-unit activity from neurons in the supplementary motor area (SMA) during a cognitive–motor (Go/NoGo) task in a monkey, both before (A) and after (B) MPTP intoxication.

Describe and **interpret** the differences observed in neuronal activity, relating your analysis to the mechanisms of akinesia in Parkinson's disease.

execution

Onset cue   instruction   Go cue   Push ⟶ Reward

Delay
1-3s

1-3s

Experimental paradigme

Push

SMA recordings

Instruction   Delay   Execution

A

B

"Attention Deficit Hyperactivity Disorder (ADHD) and comorbidities From Childhood untill Adulthood"

You are required to analyze a section of a research article that investigates the use of **functional magnetic resonance imaging (fMRI)** during a **Go/NoGo task** in adults diagnosed with **ADHD**.

Drawing on concepts discussed in the lecture, you should:

- **Explain the objectives** of the study
- **Interpret the results**
- **Discuss the study** in light of your knowledge of ADHD

1page max : Be precise and concise enough for your answer to fit on one page at most

Table 1 Baseline demographics and characteristics

	ADHD cannabis User (n=25)	ADHD cannabis Non-user (n=25)	LNCG cannabis User (n=11)	LNCG cannabis Non-user (n=12)	Overall (n=73)
Gender					
Male, n (%)	24 (96 %)	17 (68 %)	10 (91 %)	6 (50 %)	57 (78 %)
Age (yr)					
Mean (SD)	24.6 (1.4)	25 (1.2)	24.2 (1.5)	24.1 (1.0)	24.6 (1.3)

ADHD Attention-deficit/hyperactivity disorder, *LNCG* local normative control group, *SD* standard deviation, *NA* not applicable

Task and fMRI acquisition parameters

Each of the participants performed four runs of an appetitive Go/NoGo task (Somerville et al. 2011). The task consisted of responding with a right index finger button press when presented with a target (Go) cue and withholding a button press when presented with a non-target (NoGo) cue. Targets appeared in 500 ms durations with an inter-stimulus interval (ISI) jittered in duration from 2 to 14.5 s (mean 5.2 s). All four runs each contained 36 Go and 12 NoGo trials for a total of 192 trials per subject. The targets and non-targets were pseudo-randomized in presentation order within each run and defined for the participant via an instructional screen prior to the start of each run. Human faces with emotional content (Tottenham et al. 2009) (happy or neutral) were used as the primary stimulus, and fixation crosses for the ISI. The task instructions read: "Press your index finger as fast as you can whenever you see the PLAIN [HAPPY] faces. Don't press for other faces, only the PLAIN [HAPPY] faces." Each participant had, in a pseudo-randomized order, two runs of happy and two runs of neutral faces as a target. Human faces as a no-go stimulus have been well validated in prior work (Somerville et al. 2011). Echo planar images (EPI) were acquired over 154 volumes for a total of 5 m and 12 s per run (Glover et al. 2012) (TR/TE=2000 ms/30 ms, 32 axial slices, AC-PC aligned, TH=4 mm, Slice Gap=1 mm, In-plane resolution=3.4×3.4 mm). High-resolution anatomical MPRAGE T1-weighted images (TR/TE/TI=2170/5.56/1100 ms, 160 sagittal slices, TH=1.2 mm, In-plane resolution=1×1 mm) were acquired along with T2-weighted images (TR/TE= 6440/67 ms) co-planar to the functional acquisitions. For distortion correction, a dual-echo B0 mapping scan (TR/TE1/ TE2=500/3.03/5.49) was acquired co-planar with the functional acquisitions.
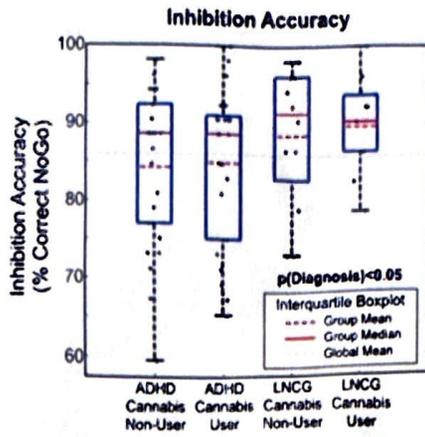
Fig. 1 In-scanner behavioral performance. A main effect of ADHD diagnosis was observed with a higher likelihood of false positives associated with ADHD (left, $p<.05$), irrespective of cannabis use history
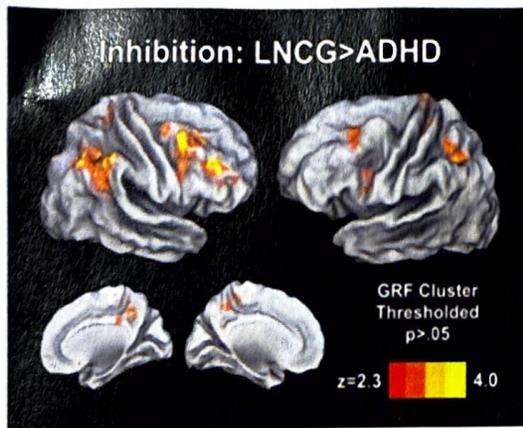

Fig. 2 Main effect of ADHD diagnosis during an inhibition (NoGo>Go) task. Cortical network differences are primarily right lateralized and include frontal and parietal regions, which are reduced in subjects with history of childhood ADHD. No regions of activation were significantly greater in ADHD than LNCG subjects

Fig. 3 Main effect of ADHD diagnosis: group map and anatomically defined subcortical ROI boxplot. Significant clusters of hypoactivation in ADHD subcortical cortices include right caudate, thalamus and accumbens (*left*). Further native space analyses confirmed right caudate hypoactivation in ADHD (*right*) participants along with right putamen and left pallidum

ROI = Region of interest
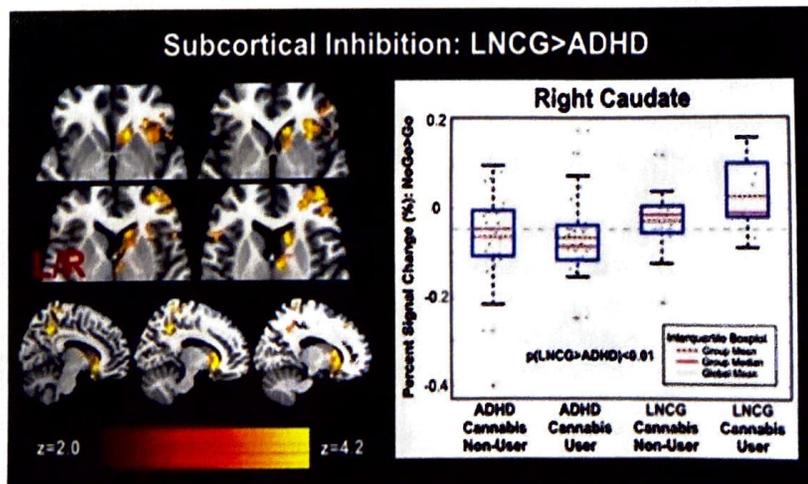
MCQ exam

Mark your answers on the answer sheet (page 2 of the second document)

1. Large human cohort studies have shown that chronic low-grade inflammation was associated with certain depressive symptoms, including:
   a) Anhedonia
   b) Fatigue
   c) Anxiety
   d) Loss of interest
   e) Motor agitation

2. In medically ill patients treated with interferon-alpha, inflammation and targeted GCH1 enzymatic pathway were associated with several biological abnormalities, including:
   a) Lowered CSF concentrations of BH4
   b) Decreased peripheral phenylalanine/tyrosine ratio
   c) Increased peripheral phenylalanine/tyrosine ratio
   d) Decreased CSF concentrations of dopamine
   e) Increased CSF concentrations of HVA

3. In depressed patients, several biological abnormalities were observed, including:
   a) Increased peripheral concentrations of neopterin
   b) Decreased peripheral concentrations of neopterin
   c) Increased peripheral concentrations of tyrosine
   d) Decreased peripheral concentrations of tyrosine
   e) Increased peripheral concentrations of tryptophane

4. In depressed patients, inflammation was related with several neuroanatomical abnormalities, including:
   a) Increased volume of the cerebellum
   b) Decreased volume of the medial prefrontal cortex
   c) Decreased thickness of the medial prefrontal cortex
   d) Increased volume of the amygdala
   e) Decreased volume of the hippocampus

5. Large human cohort studies have demonstrated that nutritional factors, including low n-3 PUFAs consumption, are associated with the development of depressive symptoms. In line with this, we have shown in depressed patients that:
   a) Peripheral EPA concentrations were positively correlated with clinical severity
   b) Peripheral DHA concentrations were negatively correlated with clinical severity
   c) Peripheral EPA concentrations were negatively correlated with clinical severity
   d) Peripheral DHA concentrations were positively correlated with clinical severity
   e) Peripheral ALA concentrations were positively correlated with clinical severity

6. In obese patients, inflammation and related IDO activation were associated with several biological abnormalities, including:
   a) Decreased peripheral concentrations of tryptophan
   b) Decreased peripheral concentrations of serotonin
   c) Decreased peripheral kynurenine/tryptophan ratio
   d) Increased peripheral kynurenine/tryptophan ratio
   e) Decreased peripheral concentrations of tyrosine

7. About the definition and classification of epileptic seizures: which answer(s) is/are correct?
   a) A generalized seizure always involves the entire cortex simultaneously.
   b) A focal seizure involves a limited cortical network, with a dynamic spatiotemporal progression.
   c) Generalized seizures may include subcortical structures.
   d) An epileptic seizure corresponds to excessive and synchronous neuronal activity.
   e) Focal seizures can never impair consciousness.

8. About epilepsy comorbidities: which answer(s) is/are correct?
   a) The risk of depression is 2 to 4 times higher in epileptic patients.
   b) Anxiety is rare in focal epilepsies.
   c) The risk of suicide is approximately sixfold higher.
   d) Cognitive disorders are rare and transient.
   e) Comorbidities are solely due to antiepileptic drug side effects.

9. About intracerebral signal analysis (SEEG): which answer(s) is/are correct?
   a) The EEG signal mainly reflects axonal action potentials.
   b) Dendritic postsynaptic potentials form the basis of the recorded signal.
   c) Low-voltage fast activity is a common marker of seizure onset.
   d) Frequency analysis cannot distinguish physiological from pathological activity.
   e) Phase coupling (phase-locking value) is a nonlinear measure of connectivity.

10. About in vitro models: which answer(s) is/are correct?
    a) They allow the study of large-scale seizure propagation.
    b) They offer precise control over the ionic and pharmacological environment.
    c) They accurately reproduce human generalized seizures.
    d) They are useful for exploring cellular pathophysiology and testing drugs.
    e) They preserve the integrity of thalamo-cortical loops.

11. About the pilocarpine model of mesial temporal lobe epilepsy: which answer(s) is/are correct?
    a) It reproduces hippocampal lesions with neuronal loss and gliosis.
    b) It induces an initial status epilepticus followed by a latent and then chronic phase.
    c) Seizures are always of the hypersynchronous type.
    d) Fast oscillations (ripples and fast ripples) characterize epileptic networks.
    e) Fast ripples (>250 Hz) are considered a pathological marker.

2

12. About GABAergic modulation in experimental models: which answer(s) is/are correct?

a) Optogenetic activation of CA3 PV interneurons has a global anti-ictogenic effect.
b) Each light stimulation of CA3 PV interneurons can paradoxically trigger a seizure.
c) The pro- or anti-seizure effect depends on the timing and intensity of stimulation.
d) Increasing GABA always prevents seizures.
e) These results illustrate the "GABA paradox" in epileptogenesis.

13. Anorexia Nervosa:

a) Is an eating disorder
b) Is accompanied by an increased drive for activity in most of patients
c) Has been recently qualified as a metabo-psychiatric disorder
d) Involves dysfunctions of the brain reward system
e) All of the above

14. Animal models of psychiatric disorders:

a) Recapitulate the whole disease
b) Can be used to study environmental and/or genetic factors
c) Are useful to dissect pathophysiological mechanisms of the diseases
d) Can be used to focus on one endophenotype of a disease
e) Possess limitations that are important to take into consideration

15. The mesolimbic dopamine pathway:

a) Is composed of serotoninergic neurons from the ventral tegmental area that project to the nucleus accumbens
b) Is composed of dopaminergic neurons from the ventral tegmental area that project to the prefrontal cortex
c) Is involved in reward-related processes and energy homeostasis
d) Is generally conserved across species of mammals
e) Is not linked to the metabolism

16. Increased activity of the D1-spiny projection neurons leads to

a) Increased motivation towards a food reward
b) Increased food intake
c) Decreased motivation towards food reward
d) Decreased food intake
e) All of the above

17. Taq1A1 polymorphism is associated with

a) Decrease Dopamine in the striatum
b) Decreased D2 dopamine receptor in the striatum
c) Increased use of fat as substrate for energy
d) Increased use of carbohydrate as fuel for energy
e) Increased impulsive behavior

18. Striatal astrocytes in obese mice control

a) Flexible behavior
b) Energy expenditure
c) Neurons calcium correlation
d) Fat metabolism
e) Fat mass

19. Ontogenesis :
a) At birth, humans have the most mature brain among mammals
b) Numerous behavior are innate
c) Innate behavior is stereotyped and spontaneously present at birth
d) Leaning of skills relies on training and observation
e) Most of our behavior relies on stereotypes routines

20. Planification of action:
a) Automatic activities rely on the spinal cord and brain stem
b) The cerebellum plays a part in procedural learning
c) Basal ganglia are not involved in learning of behavioral routines
d) The motor cortex is involved in movement parameter coding
e) The premotor cortices play a part in cognition and emotions

21. Motor cortex :
a) Most pyramidal neurons are localized in layer 4
b) This neocortex exhibits a columnar organization
c) The leg region is localized in the medial convexity
d) Pyramidal neurons encode the strength of muscular contraction
e) The pyramidal tract ends in both both ventral and dorsal horn of the spinal cord.

22. Premotor cortex
a) The lateral premotor cortex is involved in motor preparation on the basis of exteroceptive information
b) Its lesion may lead to an agnosia
c) Miror neurons play a part in learning
d) The supplementary motor area is localized on the medial surface of the cortex
e) Its lesion may lead to hyperkinetic syndromes

23. Basal ganglia
a) The striatum integrates a high number of cortical inputs.
b) Each cortico-striatal synapse is modulated by dopaminergic nigro-striatal input
c) The lenticular nucleus encompasses the caudate and the globus pallidus
d) The direct striato-pallidal pathway is involved in the inhibition of desired movements
e) The substantia nigra receives inputs from the striosomes

24. Prefrontal cortex
a) Lesions of its dorsolateral part (BA9/46) may lead to affective disorders
b) Working memory concerns spatial information
c) Broca's area (BA44) is important for speech production
d) Mental time travel relies on the media prefrontal cortex (BA9/10)
e) Lesion of the orbitofrontal cortex may lead to psychopathic behavior

25. Concerning multiple sclerosis (MS):
a) It is a neurodegenerative disease mainly affecting elderly people.
b) It mainly affects young men.
c) It is more prevalent in the southern hemisphere.
d) Its clinical course is relapsing-remitting in most patients.
e) Normal appearing brain tissue can show microstructural alterations not visible on conventional MRI.

26. **Concerning cognitive impairment in multiple sclerosis:**
   a) It can appear early in the course of the disease.
   b) It is exclusively due to focal inflammatory lesions within the hippocampus.
   c) Working memory and episodic memory are frequently impaired.
   d) Memory deficits can be associated with reduced hippocampal volume on MRI.
   e) Information processing speed is rarely affected.

27. **Concerning hippocampal alterations in MS:**
   a) All hippocampal subfields are equally affected.
   b) Activated microglia can phagocyte neurons.
   c) Complement C3 has no role in neuronal recognition.
   d) Some hippocampal subfields, such as CA1, are more vulnerable than others.
   e) Diffusion MRI cannot detect hippocampal changes because this in vivo technique is
      not sensitive enough.

28. **Concerning diffusion imaging of the brain:**
   a) It measures the Brownian motion of water molecules.
   b) It only provides information about cerebral blood flow.
   c) Fractional anisotropy (FA) values can be biased in voxels with fiber crossings.
   d) It can detect microstructural changes outside visible lesions.
   e) It provides a sensitive but nonspecific information on tissue microstructure in vivo.

29. **Considering that multiple sclerosis (MS) is a demyelinating disorder secondary to infiltration of immune cells (plaques), what could be expected from diffusion weighted imaging (DWI) in MS:**

   a) Some acute plaques could show acceleration of diffusion because of demyelination.
   b) Some acute plaques could show restriction of diffusion because of water hindrance by
      inflammatory cells.
   c) Some plaques could show acceleration of diffusion because of glial cell activation.
   d) Acceleration of diffusion, if observed, is driven by an increase of axial diffusivity
      and/or radial diffusivity.
   e) Microglia activation outside the plaques can modify diffusion metrics.

30. The figure shows diffusion encoding in individual directions and the resulting isotropic image. The corpus callosum is shown with plain arrow and the corticospinal tracts with dotted arrows. Which affirmations are correct:

First direction   Second direction   Third direction

Isotropic image
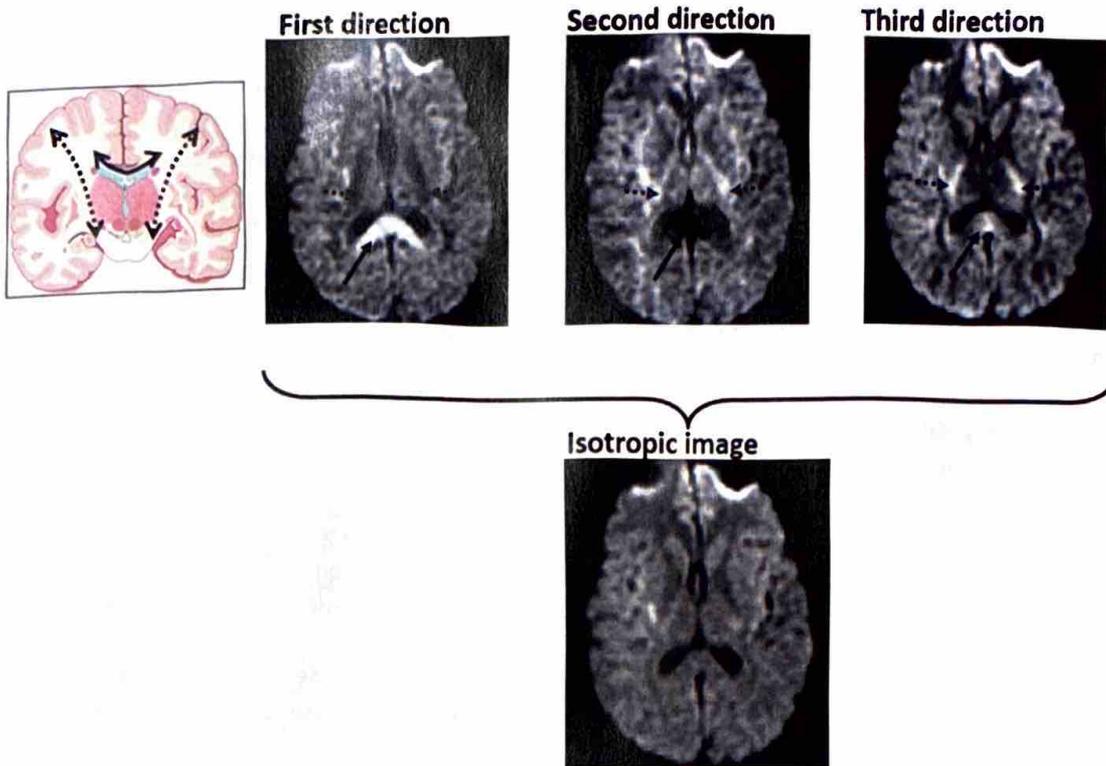
a) The first direction corresponds to a right/left gradient encoding
b) The second direction corresponds to a right/left gradient encoding
c) The diffusion signal shows water restriction of the corticospinal tracts on the third direction
d) The diffusion signal shows water restriction of the corpus callosum tracts on the second direction
e) The anisotropic effects are cancelled out on the isotropic image