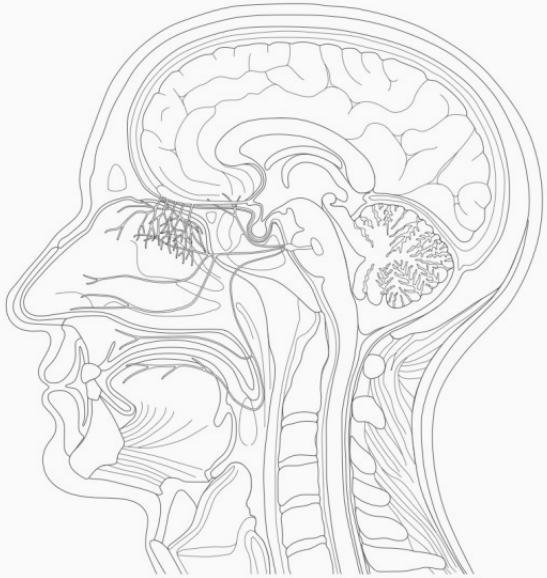
Homework - Academic Year 2023/2024

Investigating brain dopamine lateralization in Parkinson's Disease



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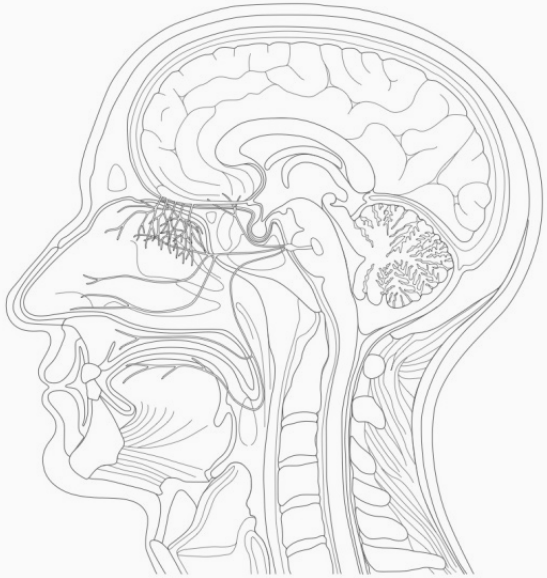
Introduction of PD



Parkinson's Disease (definition by ChatGPT)

Parkinson's disease is a progressive neurodegenerative disorder that affects movement. It is characterized by a variety of symptoms, including tremors, stiffness, slow movement (bradykinesia), and impaired balance and coordination.

The primary cause of Parkinson's disease is the loss of dopamine-producing neurons in a region of the brain called the substantia nigra. Dopamine is a neurotransmitter involved in regulating movement, and its deficiency leads to the motor symptoms associated with Parkinson's.

In addition to motor symptoms, Parkinson's disease can also cause non-motor symptoms such as cognitive changes, mood disorders (such as depression and anxiety), sleep disturbances, and autonomic dysfunction (problems with blood pressure regulation, digestion, and bladder function).

The exact cause of Parkinson's disease is not fully understood, but it is believed to involve a combination of genetic and environmental factors. While there is currently no cure for Parkinson's disease, treatment options are available to help manage symptoms and improve quality of life. These treatments may include medications, physical therapy, occupational therapy, speech therapy, and in some cases, surgical interventions such as deep brain stimulation.

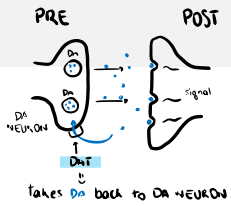
Parkinson's Disease (definition by APDA)

Parkinson's disease (PD) is a type of neurologic movement disorder, affecting the brain and causing difficulty with movements, or motor symptoms.

It is characterized by its most common motor symptoms — tremors (a form of rhythmic shaking), stiffness or rigidity of the muscles, and slowness of movement (called bradykinesia) — but also manifests in non-motor symptoms including sleep problems, constipation, anxiety, depression, and fatigue, among others, which can be present well before any visible motor symptoms. It is a chronic and progressive condition, meaning that the symptoms become worse over time and can affect the ability to perform common, daily activities.

https://www.apdaparkinson.org/what-is-parkinsons/

Rationale in brief: PD, DAT SPECT, brain asymmetry



- Parkinson's disease (PD) is characterised by the degeneration of the nigrostriatal dopamine nerve. => dopamine loss

- Dopamine transporter (DAT) single-photon emission computed tomography (SPECT) is clinically used for diagnosis of PD as biomarker for nigrostriatal dopamine degeneration.

dopamine transporters

- Generally, the evaluation of DAT-SPECT images is conducted via visual inspection, frequently supported by semi-quantitative indexes. There is the need for quantitative analysis to eliminate subjectivity and experience differences among readers.

DIAGNOSIS OF PD = DA loss

- Asymmetric hemispheric loss of dopaminergic neurons is one of the characteristic features of Parkinson's disease (PD) and could be used to support quantitative diagnostic.

Some References

https://pubmed.ncbi.nlm.nih.gov/20019219/
https://pubmed.ncbi.nlm.nih.gov/34124799/

Antonini

Outline of the homework

- The aim of the homework is to prepare a technical report that explores the value of left-right lateralization of dopamine function (if any) in Parkinson's disease using data from DAT SPECT imaging.

- **RESEARCH QUESTIONS:**

  By using a dataset derived from PPMI study, this report should address the following questions:

  PART 1 – Dopamine Brain Lateralisation in Healthy Controls

  - Is dopamine function lateralised in healthy subjects? Is there any relevant covariate associated to dopamine function lateralisation?

  ↓ see if 1 applies to PD patients from healthy

  PART 2 – Dopamine Brain Lateralisation in PD

  - Is dopamine function lateralised in PD patients? How is brain lateralisation associated to PD symptoms?

  motor symptoms, sleep problems ...

WORKFLOW

PREPROCESSING :

VARIABILI UTILI

- [x] guardare var. riassuntive (4) ⟶ NORMALIZZARE
- [x] LATERALIZZAZIONE = 3 variabili (left – right)
- [x] variabili demografiche (escludere PRIMDIAG = 97)
- [x] stessi valori variabili (0/1 ⟷ ON/OFF)
- [x] analisi missing values (dove, categorie, quanti mancano)
- [ ] GESTIONE missing values :
  - togliere soggetti (righe)
  - togliere variabili (colonne)
  - (interpolazione ?)

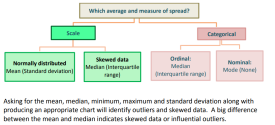
MOTIVAZIONE X REPORT: NON interpretabili x mancanza di questa informazione

⟶ SPIEGARE BENE nel REPORT perchè si è scelto di includere solo certe variabili

assumptions ⟶ TEST ⟶ results
↑ has to be INDEPENDENT
=> try to change assumptions to see how solid the results are

IDEA: sottrarre HC dalla lateralizzazione? tipo sottrarre baseline normale ?

- [x] escludere pazienti con lateralizzazione < 20 % ? ⟶ va. articolo "Ipsilateral deficits ..."
- [ ] analisi variabili importanti (mean, variance ...) ⟶ capire distribuzioni ⟶

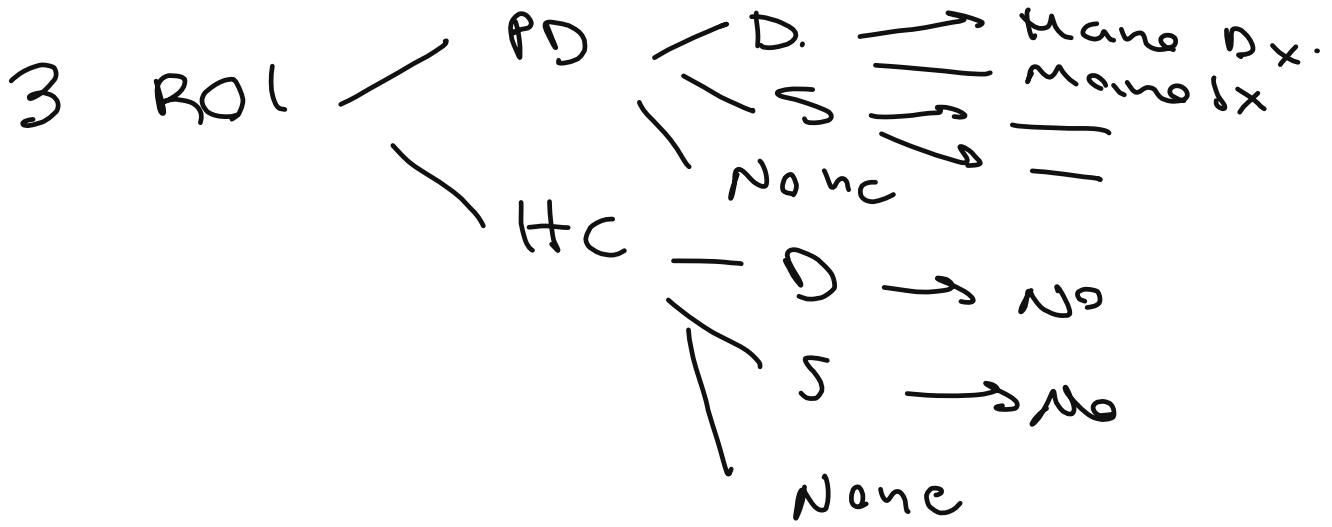


- [ ] FEATURE SELECTION (PCA, manual ... ?)
- [ ] preparare NUOVO DATASET fatto bene con SOLO le variabili e i soggetti che teniamo x analisi ?

1. Dopamine brain lateralisation in **HC** :
   - [ ] quanto/se è lateralizzata, in che regioni ⟶ [ ] TEST STATISTICI (kurtosis, skewness ...) ↳ t-test, ANOVA ...
   - [ ] COVARIATES :
     - regressione lineare
     - matrici di correlazione
   - [ ] collegamento con mano dominante

[+ altre classi oltre PD : da unire, confronto risultato ...] ?

2. Dopamine brain lateralisation in **PD**
   - [ ] quanto/se è lateralizzata, in che regioni ⟶ [ ] TEST STATISTICI (kurtosis, skewness ...) ↳ t-test, ANOVA ...
   - [ ] COVARIATES :
     - regressione lineare
     - matrici di correlazione
   - [ ] collegamento con mano dominante



LAT $\overset{Dx}{\rightarrow}$ Mano DX

LAS Sx → Mano Sx

ID

TEST STATISTICI

✓ **1-WAY ANOVA** → confronto media delle lateraliz. gruppi → H_0 : medie tutte uguali
considerando le varianze
(1 lat. alla volta)

Requisiti:

- ✓ **DISTRIBUZIONI GAUSSIANE** → Lilliefest
- **VARIANZA** uguale per tutti i gruppi **NON SERVE** ma ANOVA è ROBUSTO

- medie simili PD – HC ma sono 0
- VARIANZA PD molto + grande di HC
- => dividendo RIGHT/LEFT lat. PD non si può confrontare con HC (↙ NON HANNO LATERALIZZAZIONE)

N-WAY ANOVA → confronto 3 zone di lateralizzaz. (considera relazioni tra variabili) → magari altre var.

SCATTER PLOT →
X → DATSCAN
Y → NPTOT ...

CONFRONTO → LAT PD RIGHT/LEFT con (tutti) i sintomi

CORRELAZIONE / ANALISI lat. ↔ handed

VARIABILI :

PATNO → ID (si ripete ?)

COHORT → HC
→ PD
→ SWEDD : no evidence of dop. deficit but PD diagnosis
→ PRODROMAL : onset of PD, before diagnosis

GENETICS → cercare

ETHNICITY

HANDED

EVENT_ID → ~~BASELINE~~ : dopo screening, diagnosi effettiva
→ SCREENING : 1^ visita x entrare in uno studio, poche misure
→ NA : non gli hanno fatto la domanda?

AGE

BIRTHDATE

SEX

ANYFAMPD → familiarita'

PRIMDIAG → diagnosi primaria => modificata dopo NEWDIAGEXP
↳ da escludere 97 (SWEDD)

NEWDIAGEXP: "" → diagnosi non cambia
NA → domanda non fatta

(OTHNEURO → other neurological pathologies : sono pochi, servono?)

(DXLVL → confidence diagnosi primaria → scartare CONFIDENZA BASSA ?)

(SXDT → data inizio sintomi)

(PDDXDT → data diagnosi PD)

DX - TREMOR
diagnosi ↑
BRADY (bradykinesia)
POSINS (postural instab.)
OTHS
RIGID (rigidity)

sintomi / PD diagnosis history:
0 : NO
1 : YES ← se sono presenti già alla diagnosi
2 : UNKNOWN

UPSITFORM → versione: 1 : original, 2 : revised
UPSIT_PRCNTGE → score

UPSIT = smell identification test (sintomo PD e AD) (90%)
età, sesso = domande ⇓ punteggio

alla fine

SINTOMI

4 : severo
↑
0 : normale

NP1SLP - N night
D day
→ SLEEP PROBLEMS 27

NP1PAIN → dolore
NP1URIN → urinary problems
NP1CNST → constipation
NP1LTHD → lightheadness standing
NP1FATG → stanchezza (fatigue)

→ NP1PTOT → somma punteggi sintomi 34

+101 : unable to rate

NP1COG → cognitive impairment
NP1HALL → allucinazioni, psicosi
NP1DPRS → depressione
NP1ANXS → ansia
NP1APAT → apatia
NP1DDS → features - dopamine dysregulation sindrome
malattia: dipendenza da farmaci x dopamina

→ NP1RTOT → somma punteggi sintomi (tolto 101) 41

no 101

NP2SPCH → speech
NP2SALV → saliva + drooling
NP2SWAL → chewing + swallowing
NP2EAT → eating task
NP2DRES → vestirsi
NP2HYGN → igiene
NP2HWRT → hand writing
NP2HOBB → hobbies, activities
NP2TURN → turning in bed
NP2TRMR → tremori
NP2RISE → alzarsi
NP2FREZ → blocco camminata

→ NP2PTOT → somma punteggi sintomi 55

56

PDTRTMNT → treatment (0/1)

~~PDSTATE → functional state (ON / OFF)~~ → no effetto med.

HRPOSTMED → ore tra medicine e esame
↓
III parte test

PDMEDYN → prende medicine? (0/1)

DBSYN → ha DBS? DEEP BRAIN STIMULATION (0/1)
↓
intervento x ridurre sintomi motori PD

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DYSKPRES → dyskinesia (0/1)

DYSKIRAT → did movements interfere with rating

NHY → Hoehn & Yahr stage
(0 → 4 + 101)

97

descrive progressione PD sintomi

0 → 4 + 101

61

NP3SPCH → speech

NP3FACXP → facial expression

NP3RIG - N → neck
- RU → right arm (7)
- LU → left arm
- RL → right leg (9)
- LL → left leg

indici RIGHT

NP3FTAP - R → finger tapping right end } analisi ritmo (11)
- L → finger tapping left end

NP3HMOV - R → end movement right end (13)
- L → end movement left end

NP3-PRSP - R, - L } pronation/supination hand (15)

- TTAP - R, - L } toe tapping (17)

- LGAG - R, - L } leg agility (19)

NP3RISING → from chair

NP3GAIT → walking

NP3FRZGT → freezing gait

NP3PSTBL → postural stability

NP3POSTR → posture

NP3BRADY → bradykinesia

NP3PTRM - R, - L } postural tremor hand (27)

NP3KTRM - R, - L } kinetic tremor hand (29)

NP3RTA - R right, - L left } - U upper, - L lower } E extremity (31, 33)

NP3RTALJ → lip-jaw → REST TREMOR AMPLITUDE

NP3RTCON → consistency rest tremor

NP3TOT → somma punteggi

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HAND < R, L, mix

LAT < R, L

SYMPTOM < R, L

0 → 4 + 101 98

NP4

- WDYSK → time w/ dyskinesia
- DYSKI → funct. impact dyskinesia
- OFF → time in OFF state
- FLCTI → funct. impact motor fluctuations
- FLCTX → complexity motor fluctuations
- DYSTN → painful OFF state dystonia

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NP4TOT → somma punteggi

possiamo togliere NP4 → troppi NaN e sono poche variabili e generali

DATSCAN

NON HANNO NAN

- CAUDATE _R _L
- PUTAMEN _R _L
- PUTAMEN _R _L → _ANT

DA TOGLIERE

DATSCAN
- 0 : non compl.
- 1 : compl.
- 2 : compl. PRIMA → PREVDATDT (data)

VSINTRPT → visual interpretation
- 1 : consistent
- 2 : not consist.
- 3 : not provided

DATA ORA } SCAN

DATA ORA } iniezione → DOSE
- MBq (MEGABECQUEREL) → decay corrected total dose
- mCi (MILLICURIE) → actual total dose

} CONVERSIONE

QUALITY RATING → togliere BASSA
- 1 : buona
- 2 : ↓
- 3 : bassa

VISINTRP → maggioranza interpretazione (positive, negative) } QUALITÀ

↳ da escludere? => DAT_SCAN meno affidabili

PATIENT

- HTCM → height (cm)
- WGTKG → weight (kg)
- STARTDT → start date medication
- LEVODOPA → dose ad ogni assunzione (unità?)
- LEDD → medicina equivalente, dose giornaliera
- MCATOT → MoCA total score : MAX=30, <26 = disfunzioni cognitive ??

(Montreal Cognitive Assessment) → early detection of mild cognitive impairment

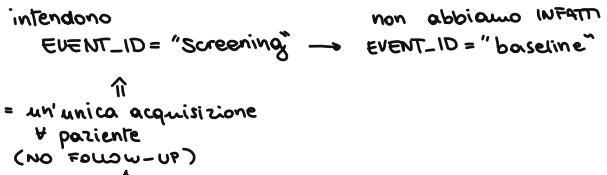
Exam questions (what I expect to see in the report)

explain why it maxes sense to explore asymmetry => see if someone has already done it => HYPOTHESIS: what do we expect to see — also see which methods have already been used

- **Background -** To introduce the **rationale** of investing brain dopamine function and potential brain asymmetry in PD.

- Main points to cover:
  - The literature evidences investigating brain (dopamine) laterization in PD
  - State the aims of the study, and based on literature evidences, formulate and motivate study hypotheses

Exam questions (what I expect to see in the report)



- **Material and Methods**

  Dataset

  - Provide a summary of the dataset (refers to data files and PPMI portal). Please note that only individual with baseline DAT imaging where included.
  - The main target regions are Caudate and Putamen, quantified as Signal Binding Ration (i.e. DATSCAN_PUTAMEN_L/R and DATSCAN_CAUDATE_L/R)

  2 ROIs

  Research methods

  - Provide a description of the methodology used to answer the research questions.
  - Provide an extensive and motivated description of statistical analysis plan, including the metrics used to assess the biomarker performances

Exam questions (what I expect to see in the report)

(ex paper = max 10 fig/tables)

- **Results** — good selection of figures and of which results to highlight
  - A clear and concise description of the statistical results providing answers to the research questions
  - A sensitivity analysis of the results to covariates, group matching and data quality (e.g. missing data, data miss-balance)

- **Discussion** ≠ repetition of results
  - Direct answers to the research questions
  - An overview of the limitations of the study
  - A list of possible suggestions to improve the study in case someone will repeat it in future

has to be = SELF-EXPLAINABLE

go question by question using hypotheses

=> COMMENTING of results (In agreement with... As expected...)

maybe missing data

Deliverables

Expected deliverables (i.e. what you have to submit) consist in

- A technical report (pdf file)
- A zip folder with all the code used the process the data and ancillary files (make sure it contains all the information for re-using it)

SUBMISSION RULES

- Max Four members per group [choose your team wisely]
- Submission date: Sunday 16th June at midnight

Marking: PROJECT REPORT MARKING GRID file

Element	Content	Maximum Mark
Abstract	• Summary of the work presented in the report (a summary figure is welcome) • Clarity of writing • Shows awareness of the limitations and significance of the work	10
Background	• Clarity of statement of aims and hypothesis to be tested • Range and appropriateness of background material and/or references • Clarity of writing including presentation and organisation of material • Analysis and summary of background material	15
Materials & Methods	• Correct description of materials and their sources (e.g. study sample etc.) • Clarity of description of methods and appropriate level of detail such that someone else could repeat the experiments or study • Correct statistical planning	15
Results	• Results or data presented in a logical order and containing all the relevant information • Presentation of data including appropriate use of graphs/illustrations such as micro photographs with appropriate figure legends or statistical analysis with correct labelling in each case • Clarity of written description and of experimental work and results • Correct interpretation of findings	30
Discussion	• Quality of conclusions drawn from the data • Comparison with the literature where appropriate, and appropriate referencing • Analysis and insight • Discussion of future work	15
Figures	• Correct presentation • Quality and quantity • Relevance	5
References	• Correct presentation • Quality and quantity • Relevance and recency	5
Code	• Clarity of the code and presentation • Reproducibility	5
		100