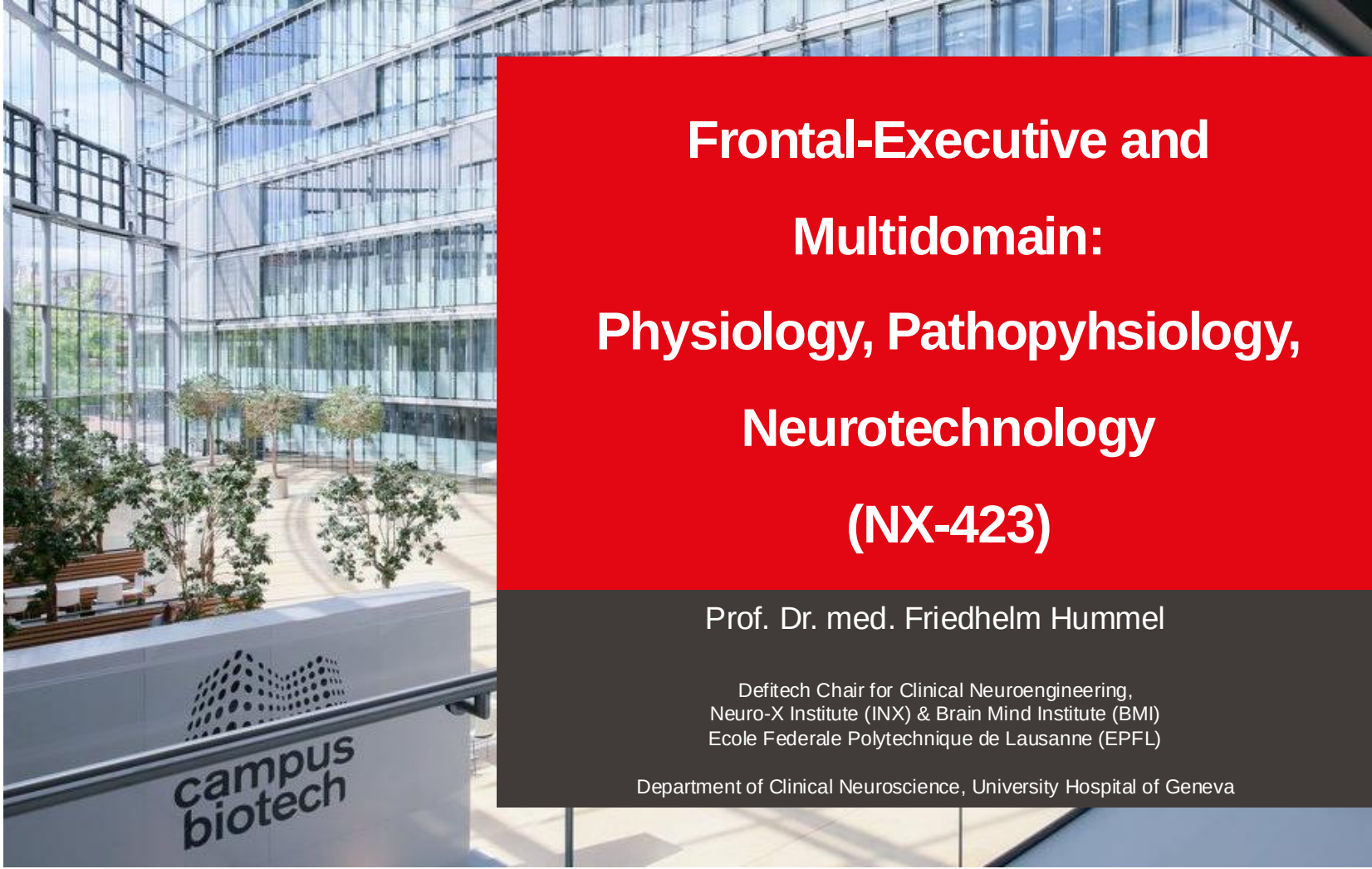
EPFL

Neuro X Institute

HUG Hôpitaux Universitaires Genève

Clinique romande de réadaptation



Frontal-Executive and Multidomain: Physiology, Pathopyhsiology, Neurotechnology (NX-423)

Prof. Dr. med. Friedhelm Hummel

Defitech Chair for Clinical Neuroengineering,
Neuro-X Institute (INX) & Brain Mind Institute (BMI)
Ecole Federale Polytechnique de Lausanne (EPFL)

Department of Clinical Neuroscience, University Hospital of Geneva

Neuro-X Master:

NX-423
Translational neuroengineering

Learning Goals - Outline

Frontal-executive functions

- Key brain regions and their functions
- How to objectivize frontal-executive functions
- Focus on motivation and dysfunction of motivation
- Brain correlates
- Conceptulization
- Apathy

High-level cognitive processes that enable goal-directed behavior, decision-making, and problem-solving.

Prefrontal Cortex (PFC)

- **Dorsolateral Prefrontal Cortex (DLPFC) to (dorsal) striatum**
  - Working memory, cognitive flexibility, reasoning.
  - Dysfunction linked to obsessive-compulsive disorder (OCD) and schizophrenia

- **Ventromedial Prefrontal Cortex (VMPFC)**
  - Emotional regulation, value-based decision-making.
  - Dysfunction linked to Apathy, Impulse Control Disorders (Pathological Gambling, Compulsive Shopping, Binge Eating), Anxiety Disorders, Post-Traumatic Stress Disorder (PTSD)

- **Orbitofrontal Cortex (OFC) to (ventral) striatum**
  - Social cognition, impulse control, reward value, reinforcement learning
  - Dysfunction linked to Frontotemporal Dementia, Attention-Deficit Hyperactivity Disorder (ADHD), Addiction

Anterior Cingulate Cortex (ACC)

- Role in monitoring conflicts and error detection.
- Importance in adaptive decision-making and response inhibition.
- impairs motivation and contributes to apathetic syndromes

Striatum: striatum is the largest subcortical structure of the basal ganglia and is divided into

- **Dorsal striatum** (caudate nucleus & putamen) – involved in cognitive and motor control.
- **Ventral striatum** (including the **nucleus accumbens**) – crucial for motivation and reward processing.
- Receives extensive glutamatergic projections from the PFC, which governs executive functions, forming a key component of cortico-striatal-thalamic loops.

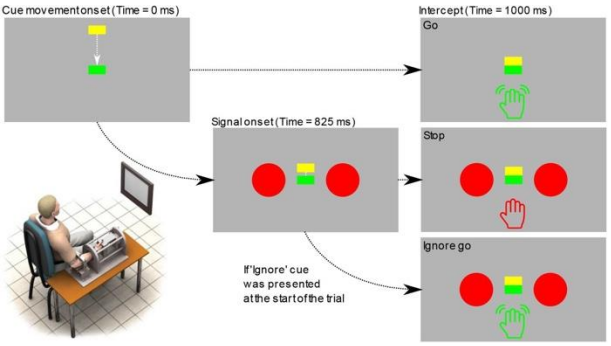
- Neurotransmitter Involvement

  - Dopamine (DA): A major modulator of striatal function, affecting cognitive control and reinforcement learning. High dopamine → promotes flexible, goal-directed behavior. Low dopamine → leads to cognitive rigidity (as seen in Parkinson's disease).

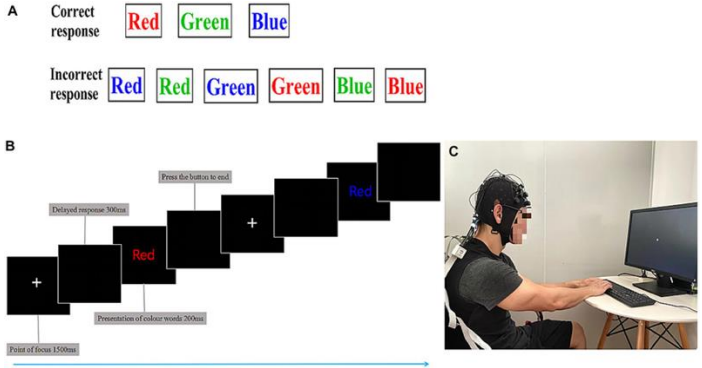
  - Glutamate: Drives excitatory inputs from the frontal cortex to the striatum.
  - GABA: Inhibitory output to refine decision-making processes.

- The striatum is not just a motor hub—it is a core component of executive function, shaping cognition through reward processing, cognitive flexibility, and behavioral control.

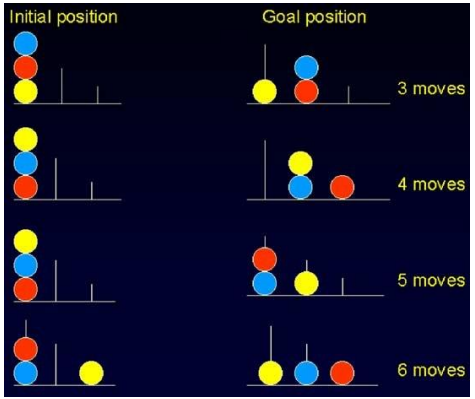
Go/No-Go Task:
Response inhibition



Stroop Task:
Cognitive flexibility and interference control.



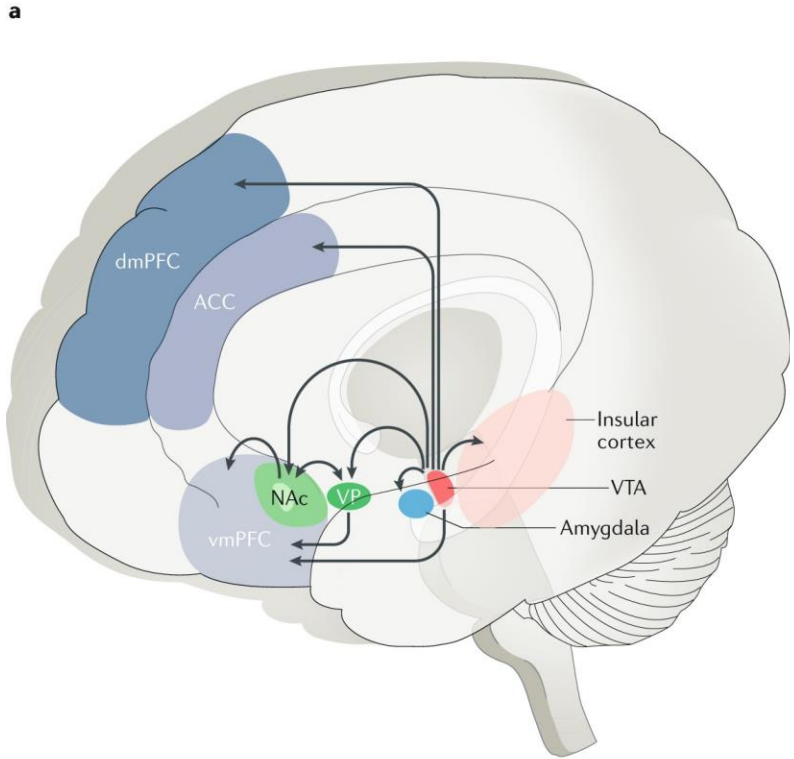
Tower of London Task:
Planning



Motivation:

the **energizing of behavior** in pursuit of a **goal**, is a fundamental element of our interaction with the world and with each other. **All animals** share motivation to obtain their **basic needs**, including food, water, sex and social interaction.

Frontal-executive functions **– motivation**

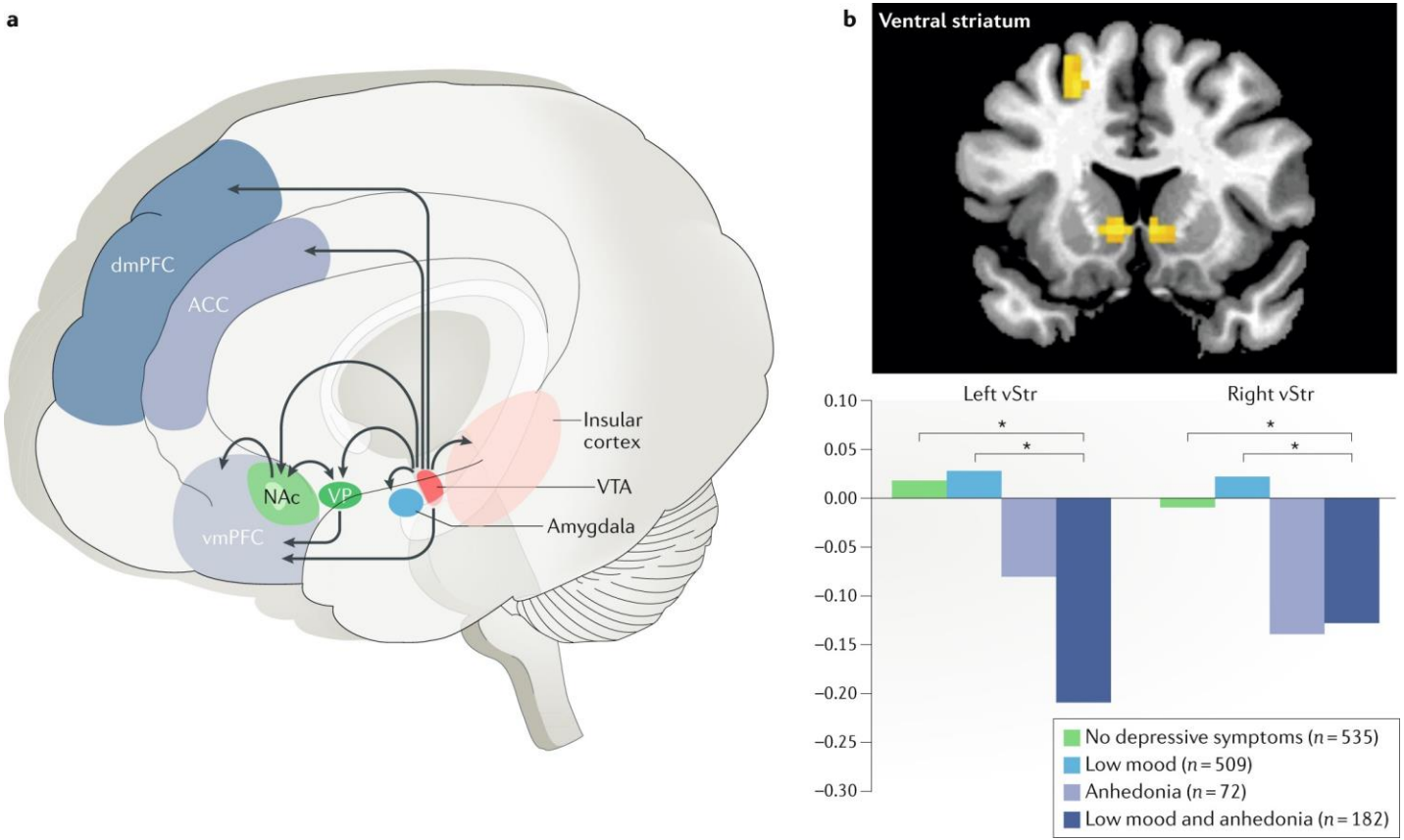


Frontostriatal circuits implicated in **motivation** to act for **rewards** and **effort-based decision making** include the **dopaminergic** projection from the ventral tegmental area (**VTA**) to the ventral striatum (**vStr**), which includes the nucleus accumbens (**NAc**) and ventral pallidum (**VP**).

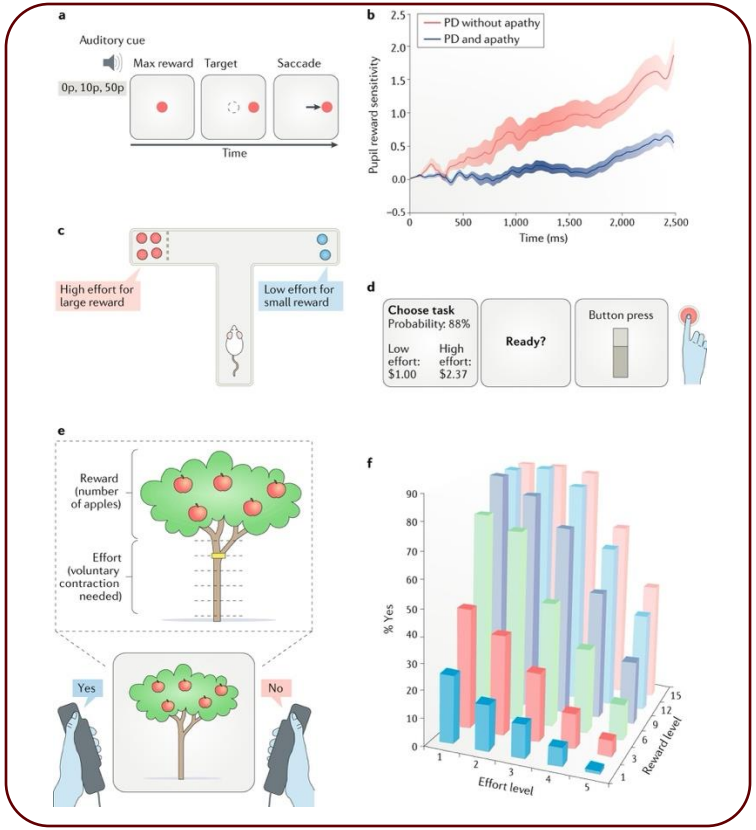
Striatal regions **project**, via the thalamus, to different parts of the **medial prefrontal cortex**, including the ventromedial prefrontal cortex (**vmPFC**), dorsomedial prefrontal cortex (**dmPFC**) and the anterior cingulate cortex (**ACC**).

These regions in turn project back to the basal ganglia.

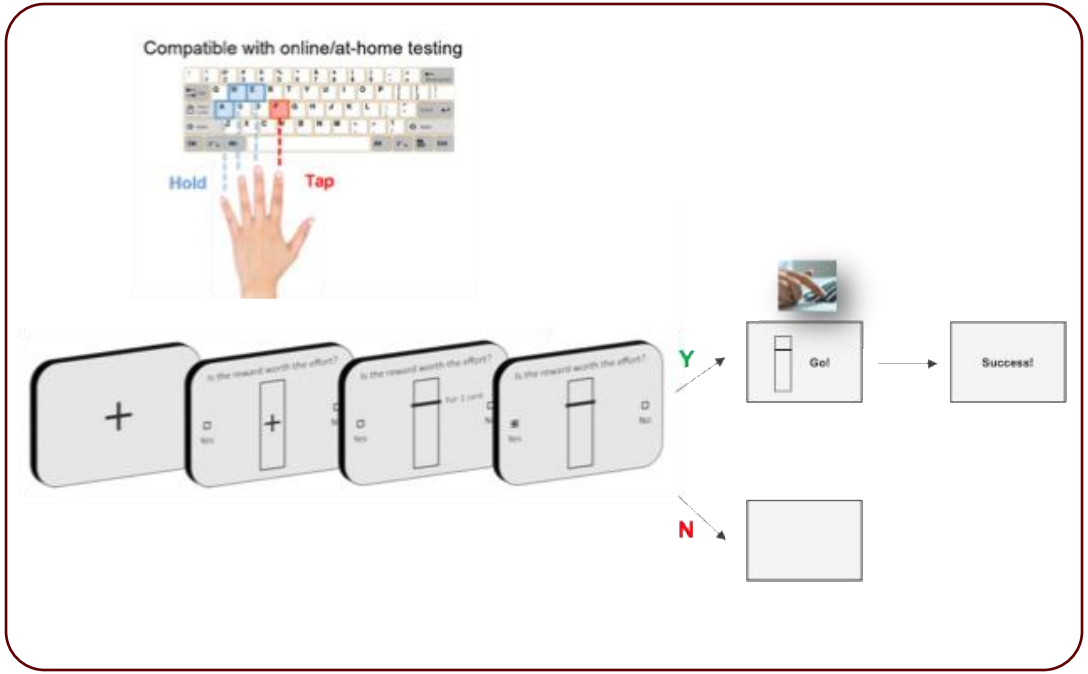
Husain & Roiser 2018


a
dmPFC
ACC
Insular cortex
NAc
VP
VTA
Amygdala
vmPFC
b
Ventral striatum
Left vStr
Right vStr
0.10
0.05
0.00
−0.05
−0.10
−0.15
−0.20
−0.25
−0.30
*
*
*
*
No depressive symptoms (n = 535)
Low mood (n = 509)
Anhedonia (n = 72)
Low mood and anhedonia (n = 182)

Effort-Based Decision Making: Evaluating reward vs. effort

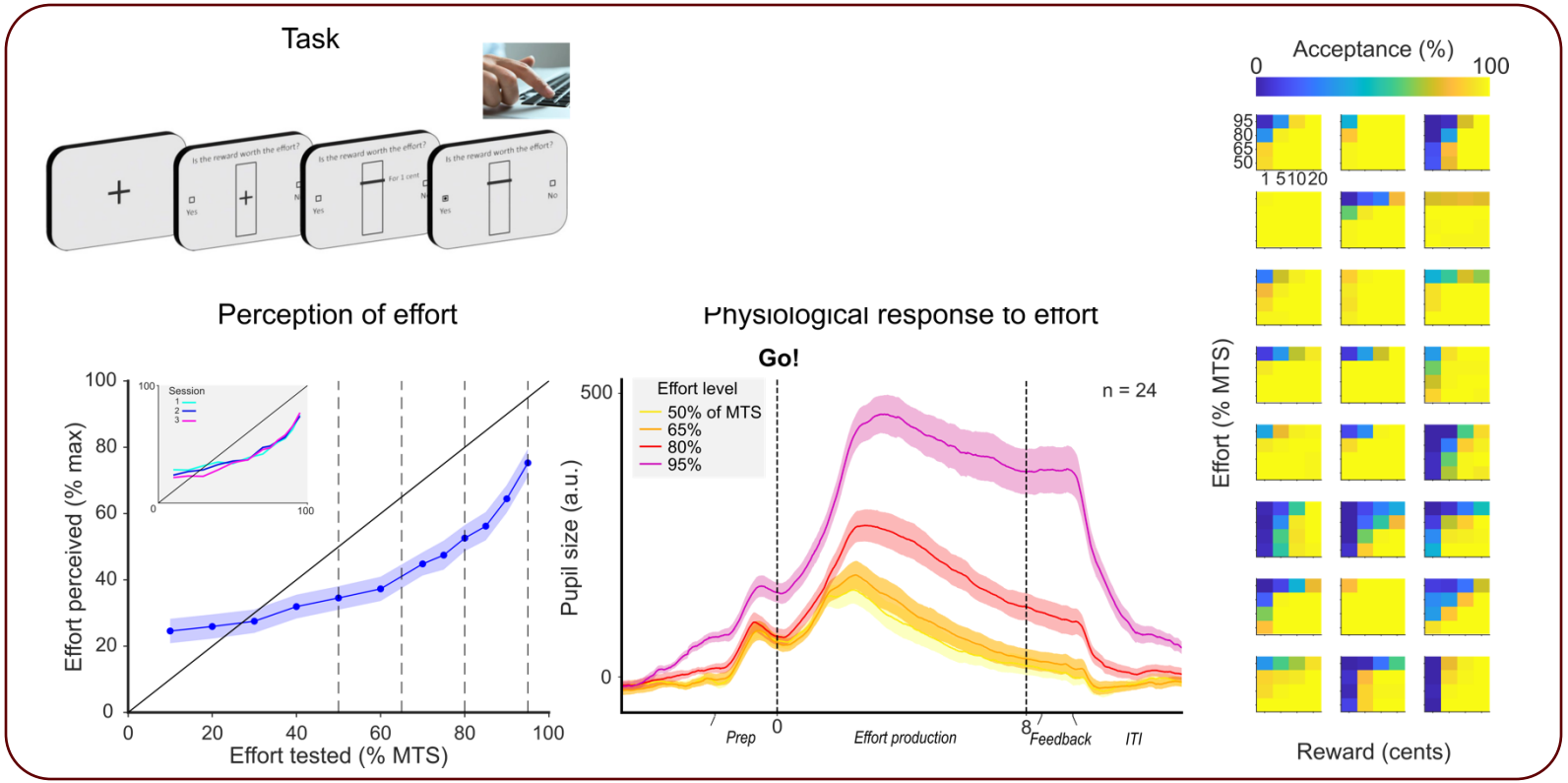


Husain & Roiser 2018



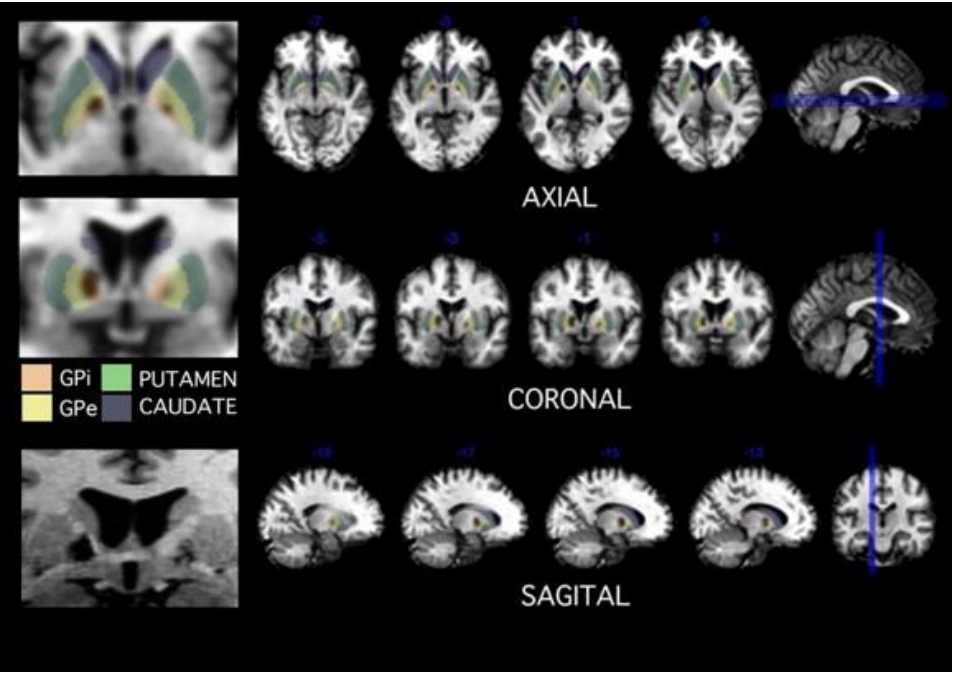
Vassiliadis et al. under review

Effort-Based Decision Making: Evaluating reward vs. effort



Vassiliadis et al. under review

Frontal-executive functions: **Loss of Motivation - Apathy**



Apathy – a syndrome charaterized by a loss of motivation

Reduction of **goal-directed** behavior either in behavioral/cognitive, emotional or social dimenesions in compariosn to patients' previous level of fucntioning

2 out of the following 3 domains affected (>4weeks)
- Behavior and cognition (e.g., making choices)
- Emotion (e.g., empathy)
- Social interactions (e.g., relationships)

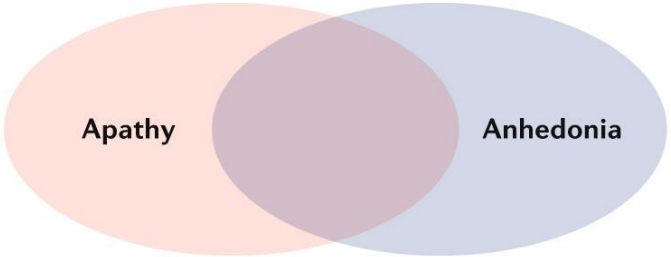
Adam *et al.* 2013

For details Robert *et al.* 2018 Eur Psych

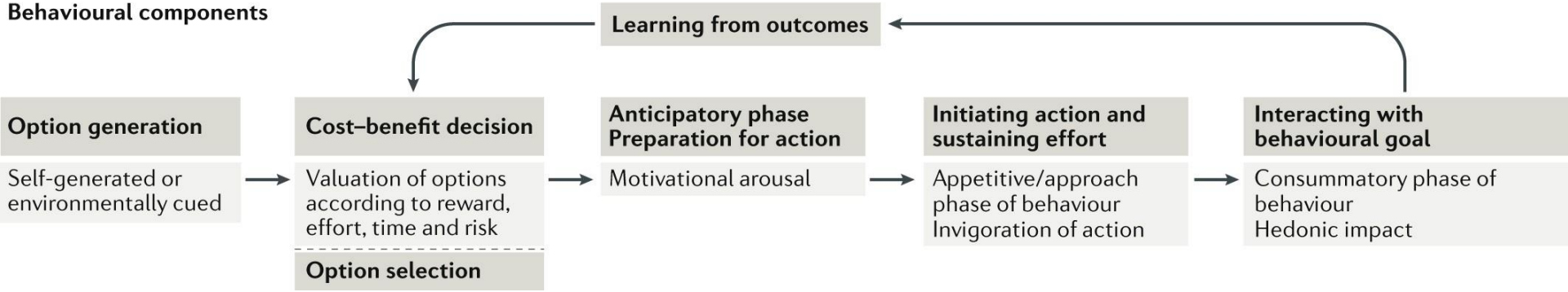
Frontal-executive functions: Loss of Motivation

Why do we do what we do?
A framework for motiviation to action and a loss of motivation in apathy

Syndrome



Behavioural components



Husain & Roiser 2018

Frontal-executive functions: **Apathy**

- **Impaired motivation** and consequent reduced goal-directed behavior
- Large impact on **quality of life** and **no established treatment**
- **Multidimensional**: impacts cognition, psychosocial interactions, engagement in rehabilitation → influence prognosis
- **Transdiagnostic** syndrome with **high prevalence**

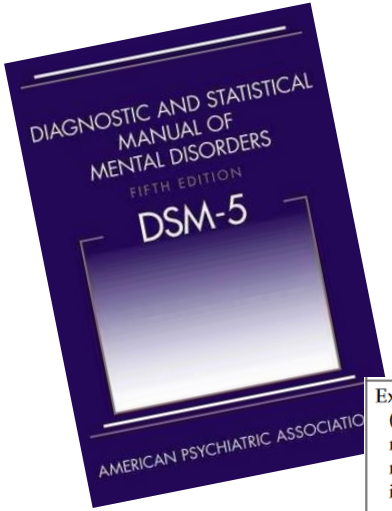
Disorder	Apathy in population (%)
Alzheimer's disease	49
Frontotemporal dementia	72
Huntington's disease	47
Major depressive disorder	38
Parkinson's disease	40
Schizophrenia	47
Stroke	36
Traumatic brain injury	61
Vascular dementia	65

Husain & Roiser 2018

Take-home messages/To know

- ✓ cognitive processes that enable goal-directed behavior, decision-making, and problem-solving
- ✓ Key brain areas involved in frontal-executive functions
- ✓ Tasks to determine objectively frontal-executive functions
- ✓ Motivation and dysfunction of motivation (Apathy)

"Neurocognitive Disorder"



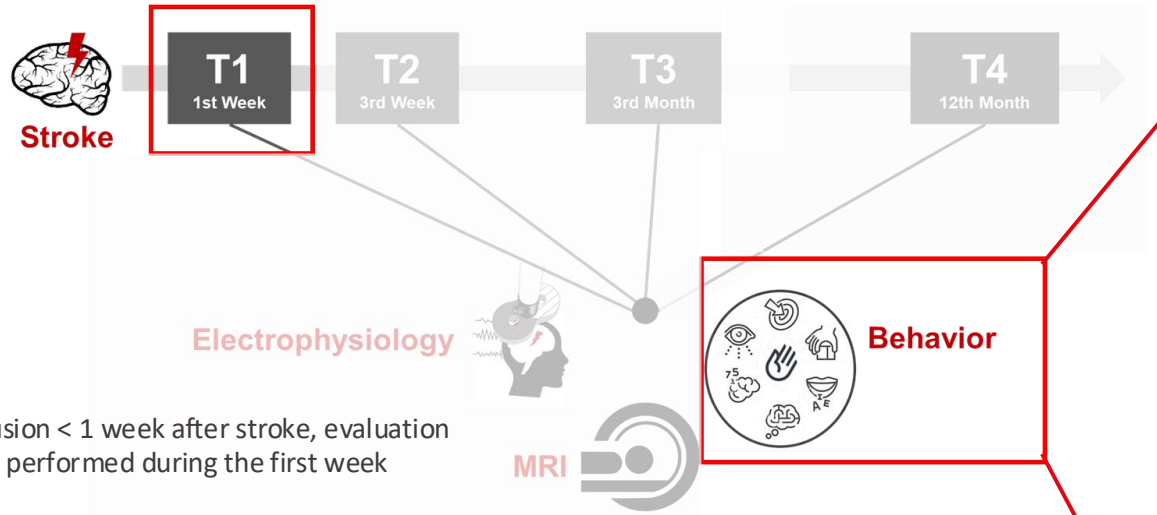
*Evidence of **significant cognitive decline** from a previous level of performance in one or more cognitive domains (complex attention, **executive function**, learning and memory, perceptual-motor or social cognition)*

- *Concern of the individual*
- *Interference with independence in everyday activities*
- *Not occurring during delirium, not explained by another mental disorder (e.g. depression)*
- *Documented by standardized neuropsychological testing*

Executive function (planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility)	*Major:* Abandons complex projects. Needs to focus on one task at a time. Needs to rely on others to plan instrumental activities of daily living or make decisions. *Mild:* Increased effort required to complete multistage projects. Has increased difficulty multitasking or difficulty resuming a task interrupted by a visitor or phone call. May complain of increased fatigue from the extra effort required to organize, plan, and make decisions. May report that large social gatherings are more taxing or less enjoyable because of increased effort required to follow shifting conversations.	*Planning:* Ability to find the exit to a maze; interpret a sequential picture or object arrangement. *Decision making:* Performance of tasks that assess process of deciding in the face of competing alternatives (e.g., simulated gambling). *Working memory:* Ability to hold information for a brief period and to manipulate it (e.g., adding up a list of numbers or repeating a series of numbers or words backward). *Feedback/error utilization:* Ability to benefit from feedback to infer the rules for solving a problem. *Overriding habits/inhibition:* Ability to choose a more complex and effortful solution to be correct (e.g., looking away from the direction indicated by an arrow; naming the color of a word's font rather than naming the word). *Mental/cognitive flexibility:* Ability to shift between two concepts, tasks, or response rules (e.g., from number to letter, from verbal to key-press response, from adding numbers to ordering numbers, from ordering objects by size to ordering by color).

*Alzheimer's disease, Frontotemporal lobar degeneration, Lewy body disease, **Vascular disease,** Traumatic brain injury, substance/medication use, HIV, Parkison's disease, Huntington's disease….*

NCD in Stroke : TiMeS Project



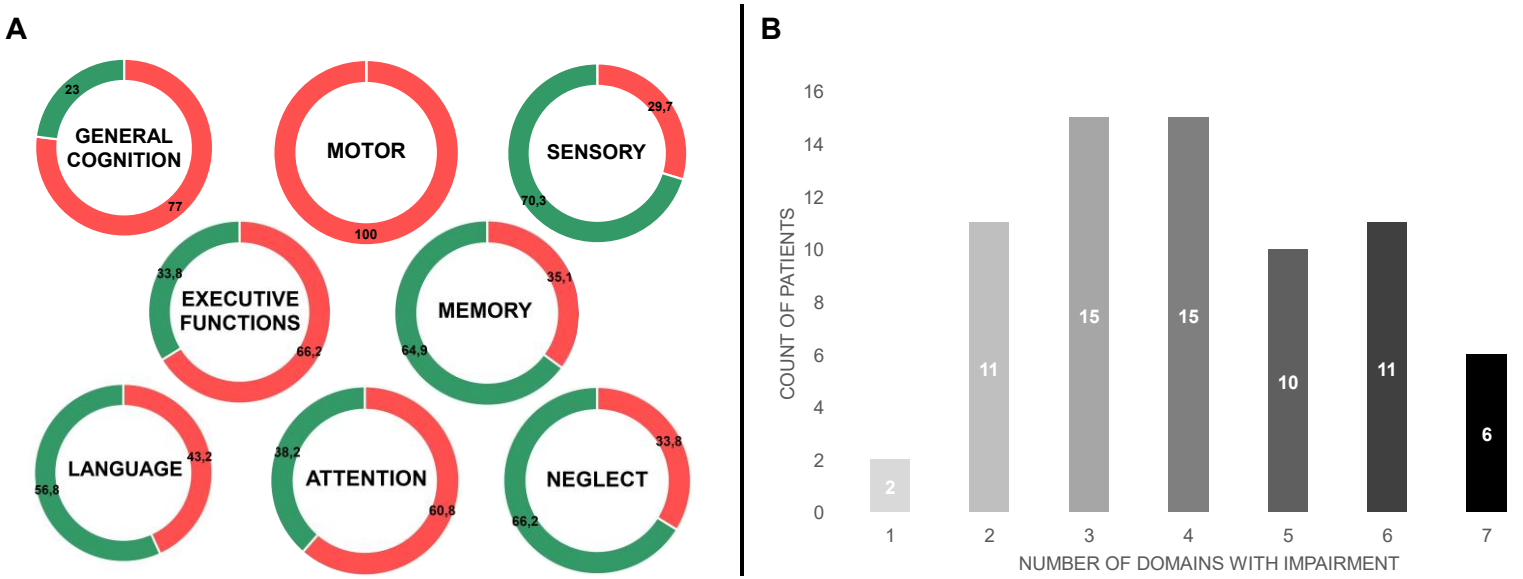
Inclusion < 1 week after stroke, evaluation performed during the first week

- Motor
- Sensory
- Neglect
- Language
- Attention
- Memory
- Executive functions
- Anxiety Depression
- Fatigue

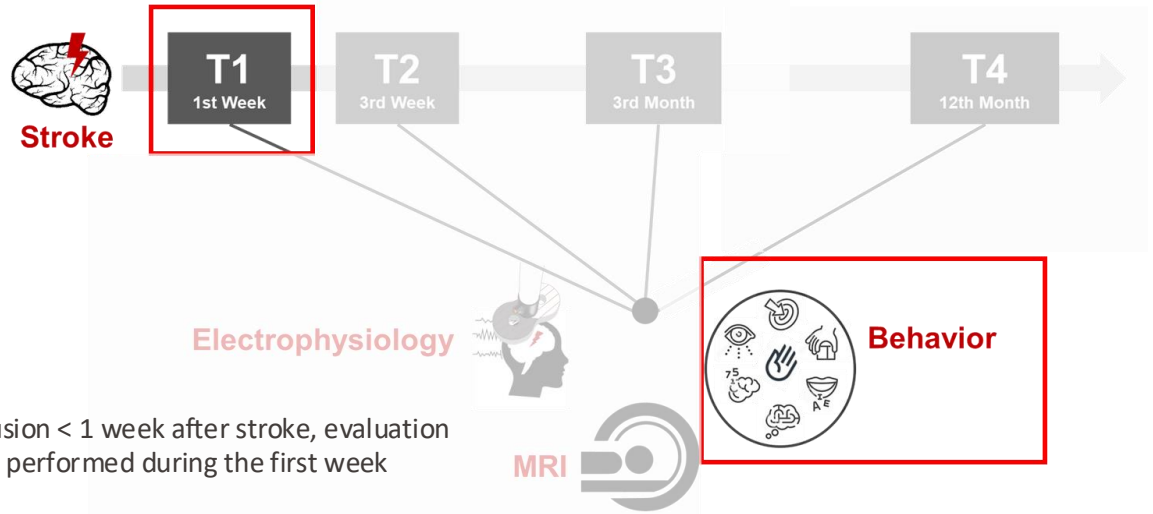
In-detail and multi-domain evaluation with 50+ tests, clinical scales and questionnaires

NCD in Stroke : TiMeS Project

Multi-domain deficits in patients selected for a paresis



TiMeS Project



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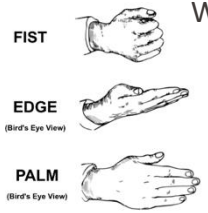
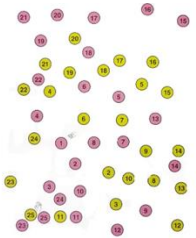


Working memory, inhibitory control, cognitive flexibility

YELLOW BLUE ORANGE
BLACK RED GREEN
PURPLE YELLOW RED
ORANGE GREEN BLUE
BLUE RED PURPLE
YELLOW RED GREEN

Sequences
5, 8, 2
6, 9, 4
6, 4, 3, 9
7, 2, 8, 6
4, 2, 7, 3, 1



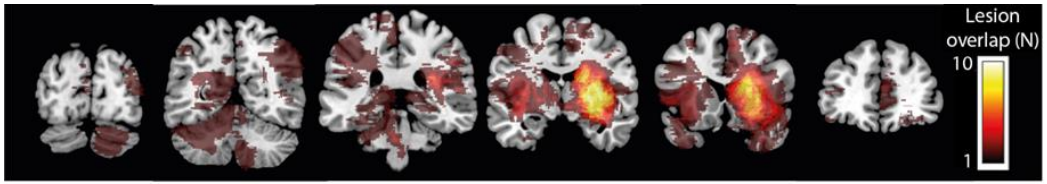
Frontal Assessment Battery, Stroop Test, Color Trail Making test, Digit Span, Bimanual coordination…

TiMeS – Patients characteristics

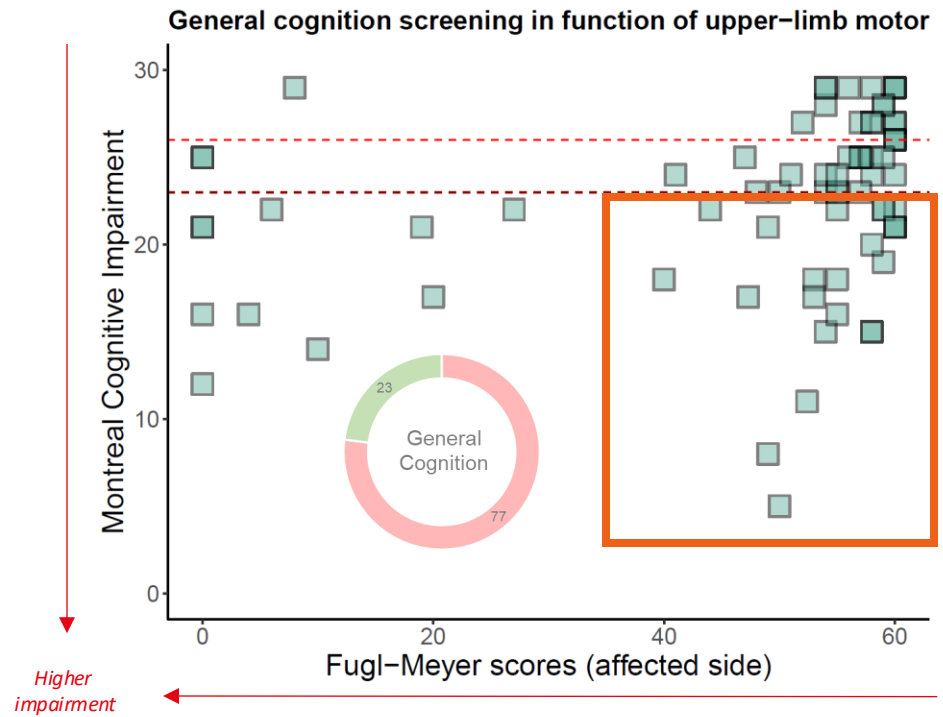
- Principal inclusion criteria: **upper-limb motor deficit**
- **Age = 67,3 ± 13,3, males = 69%**
- Days since stroke at inclusion : median **day 5** (day 1- day 12)

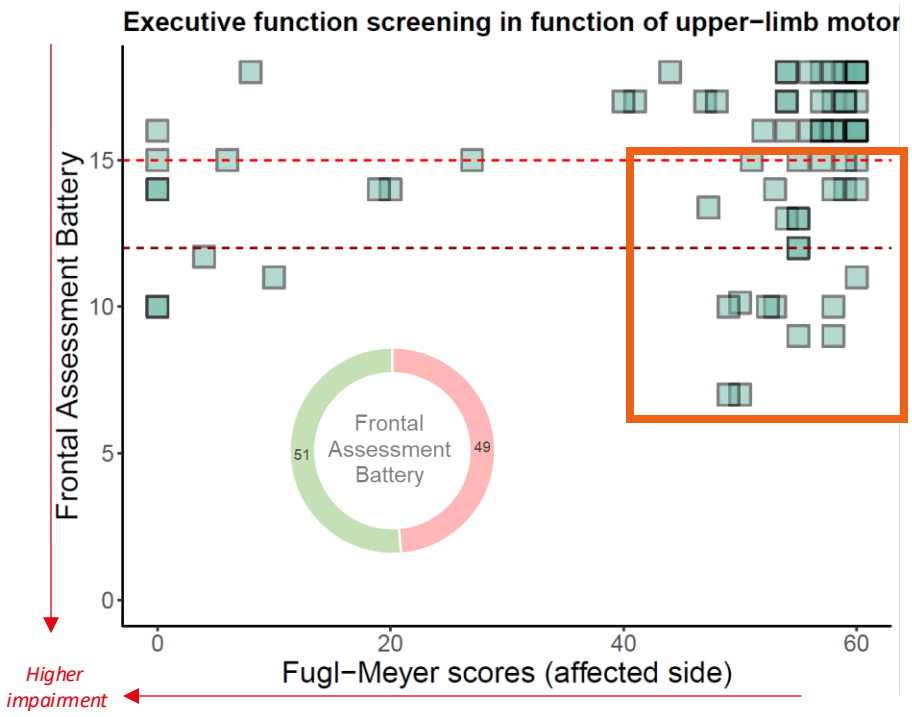
Ischemic stroke : 96%
First-ever stroke : 86,5 %
Right hemisphere affected : 55%
NIHSS : 5 (0-24)

Cortical : 6,8 %
Subcortical – mixed : 73 %
Cerebellum : 4%
Brainstem : 14,9%



TiMeS cohort & cognitive deficits

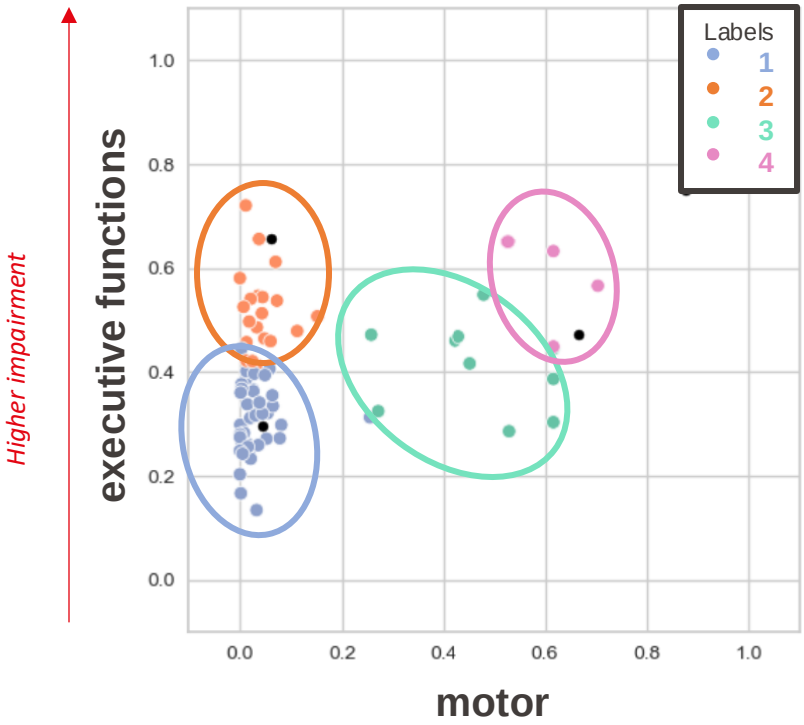




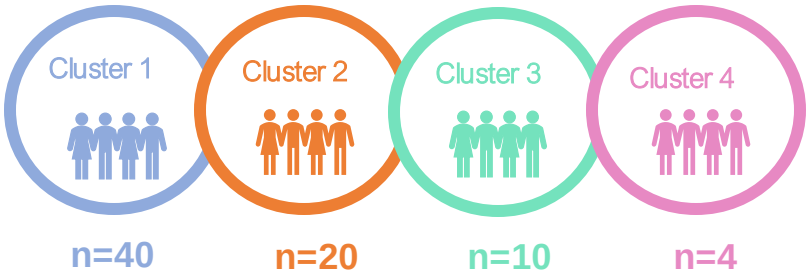
Substantial proportion of patients with impaired cognition and **executive dysfunction** even when motor deficit is mild

Motor/Cognitive-based clustering

K-means clustering (*based on motor, attention, executive functions, sensory, language*)

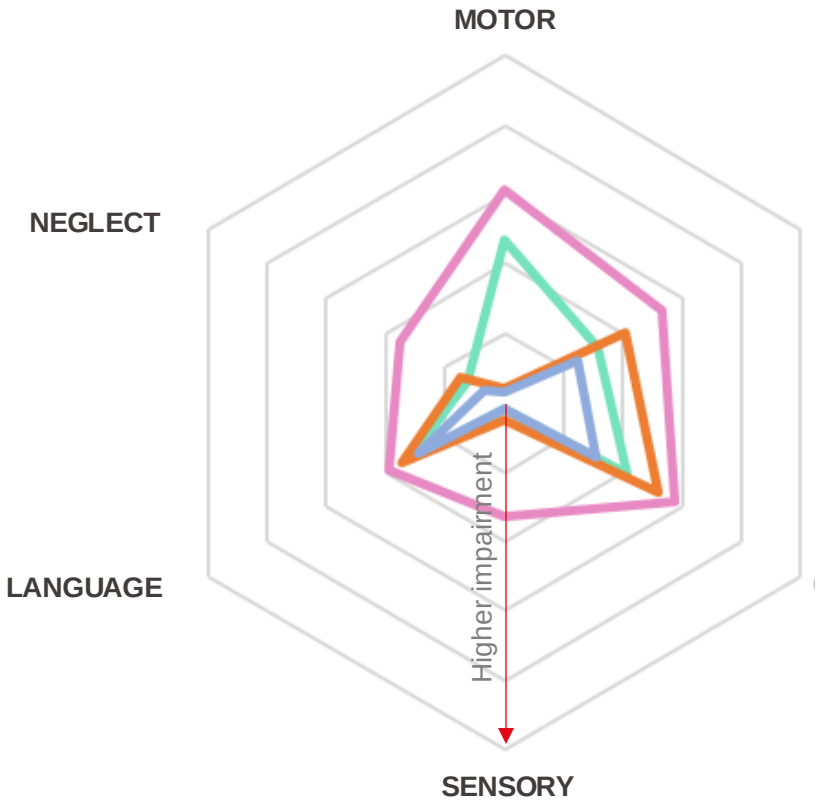


4 clusters identified



Multi-domain behavioral profiles?

Motor/Cognitive-based clustering



Cluster 1
n=40

Largest cluster
Least impaired
Reference cluster

Cluster 2
n=20

Large cluster
More impaired in non-motor domains
Slightly impaired in motor function

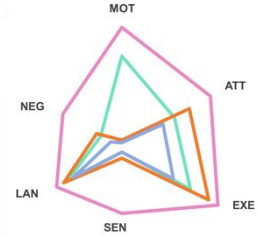
Cluster 3
n=10

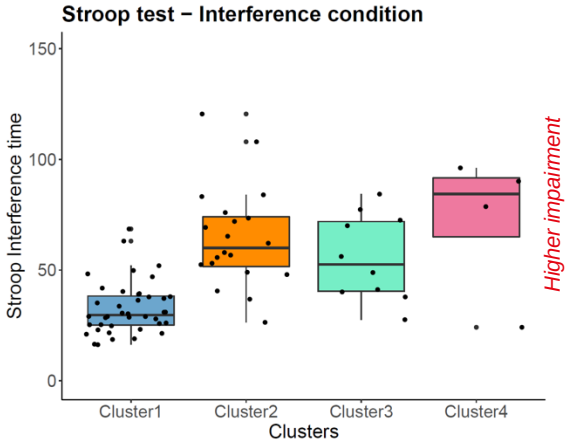
Smaller cluster
More impaired in **motor function**

Cluster 4
n=4

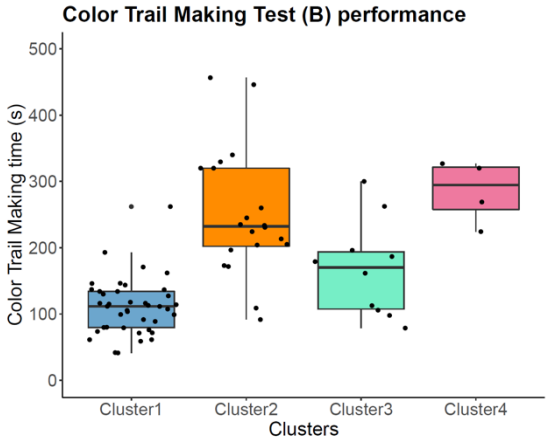
Smallest cluster
Largest multi-domain impairment

Executive dysfunction / clusters

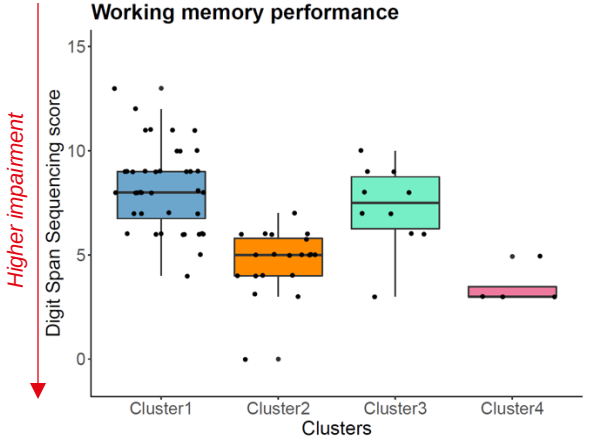




Higher impairment



Higher impairment



YELLOW BLUE ORANGE
BLACK RED GREEN
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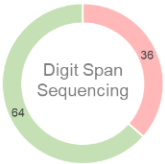
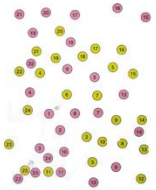
BLUE RED PURPLE
YELLOW RED GREEN





Sequences

5, 8, 2	2, 5, 8
6, 9, 4	4, 6, 9
6, 4, 3, 9	3, 4, 6, 9
7, 2, 8, 6	2, 6, 7, 8
4, 2, 7, 3, 1	1, 2, 3, 4, 7

Take-home messages

- ✓ Substantial incidence of cognitive impairment in acute stroke patients, reflected by **executive dysfunctions**
- ✓ Subgroup of patients with mild stroke/low motor impairment but **large executive deficits,** impaired in all aspects of this domain
- ✓ **Executive dysfunction** impacts **quality of life, return to work, social life**, and could **slow down recovery** in other domains (e.g. motor, language)

Impact of technological developments?

Brain stroming in class