Why not try harder?

Computational approach to motivation deficits in neuro-psychiatric diseases.

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Université Paris Cité – GHU Paris Psychiatry & Neurosciences (Sainte-Anne Hospital)

Motivation Brain Behavior (Paris Brain Institute)

Disclosure of Interests

Clinical trial (research support)	Lundbeck SAS, LivaNova
Consulting; Medical and scientific advice	Les laboratoires Servier, Otsuka Pharmaceutical SAS, Recordati, Lundbeck SAS
Speaker at conferences	Les laboratoires Servier, Lundbeck SAS, Otsuka Pharmaceutical SAS, LivaNova, Janssen, Chiesi
Invitation to conferences	Les laboratoires Servier, Lundbeck SAS, Otsuka Pharmaceutical SAS, Janssen

Definition of motivation

- Motivation is a concept used by an observer to understand the behaviour of an agent :
  - Motivation as a content = the goal (an anticipated world state)
  - Motivation as a process = adapts behaviour direction and intensity to the goal
  - Motivation as a state / trait = a description of the agent

Definition of motivation

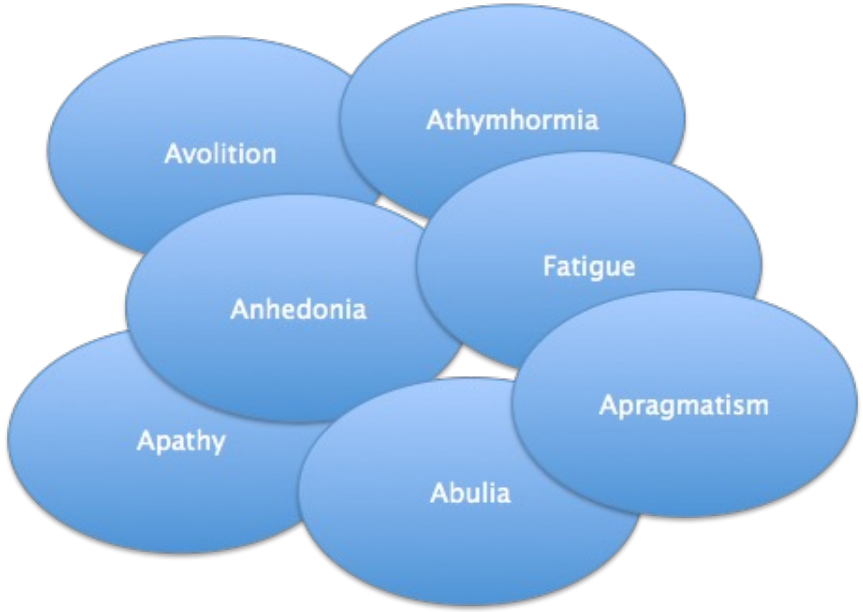
Direction

Intensity

Motivation deficit

Motivation deficit… and psychiatry

- DSM - 5 criteria :
  - Schizophrenia : a decrease in motivated self-initiated purposeful activities
  - Depression : markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
  - Manic episode : increase in goal-directed activity



Why is it important ?

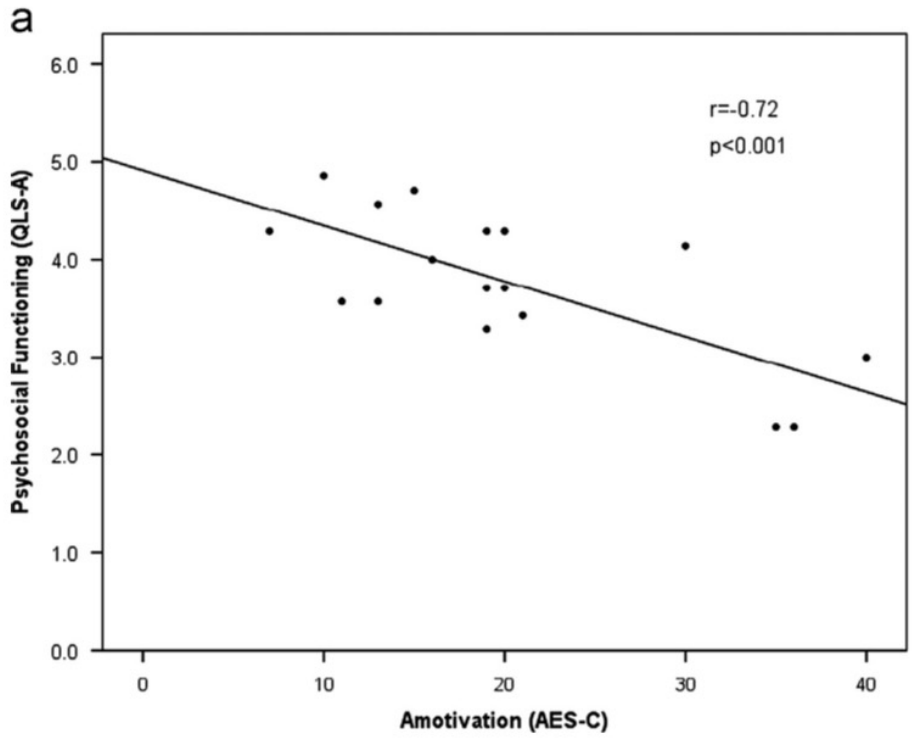
Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 1–10

DOI: 10.1111/acps.12289

ACTA PSYCHIATRICA SCANDINAVICA



Bowi, 2006, Foussias 2011, Konstantakopoulos, 2011, Fervaha 2013, 2014, Faerden 2009, Lam, 2015 and many others…

Available online at www.sciencedirect.com

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Comprehensive Psychiatry 66 (2016) 31–38

COMPREHENSIVE PSYCHIATRY

www.elsevier.com/locate/comppsych

Motivational deficits in major depressive disorder: Cross-sectional and longitudinal relationships with functional impairment and subjective well-being

Gagan Fervaha[a,b,*], George Foussias[a,b,c], Hiroyoshi Takeuchi[a,c], Ofer Agid[a,b,c], Gary Remington[a,b,c]

[a]Schizophrenia Division and Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Canada
[b]Institute of Medical Science, University of
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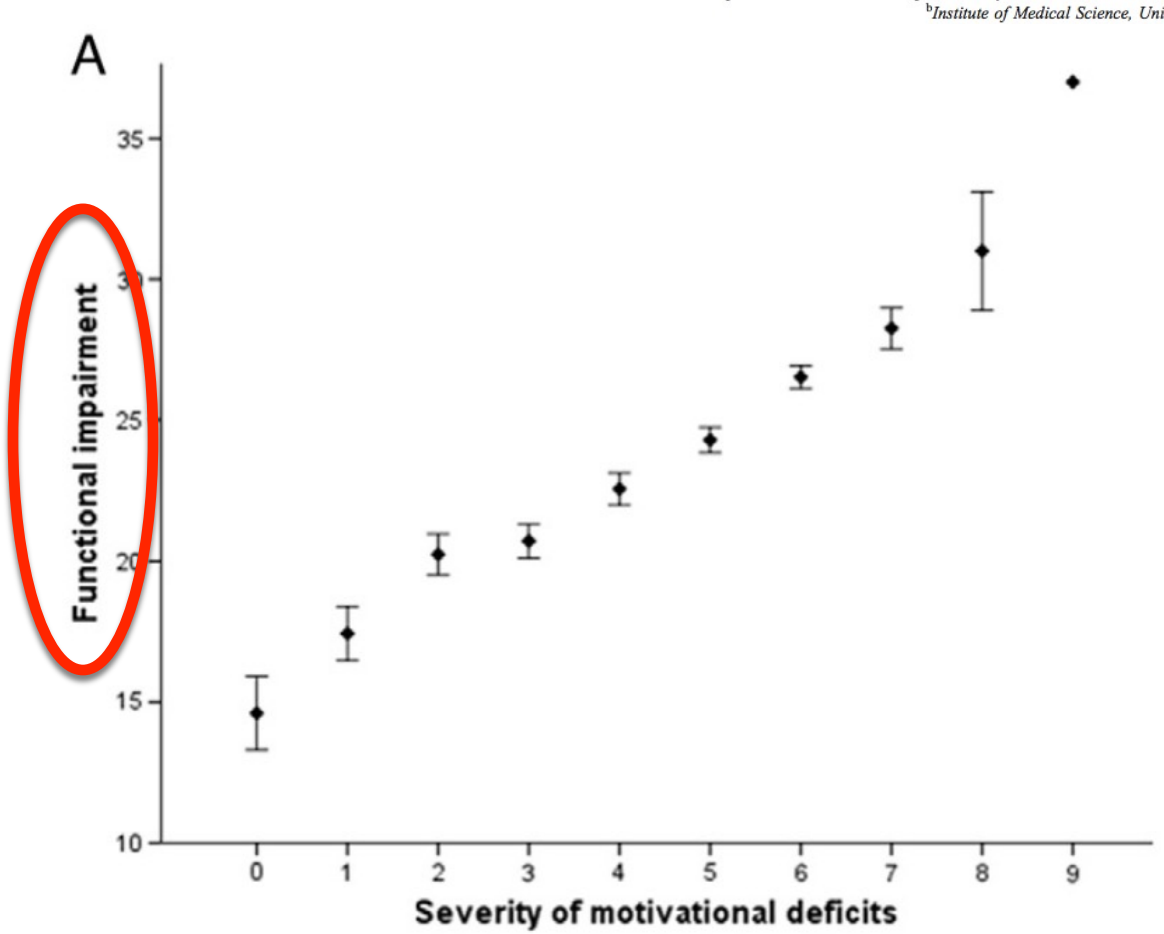
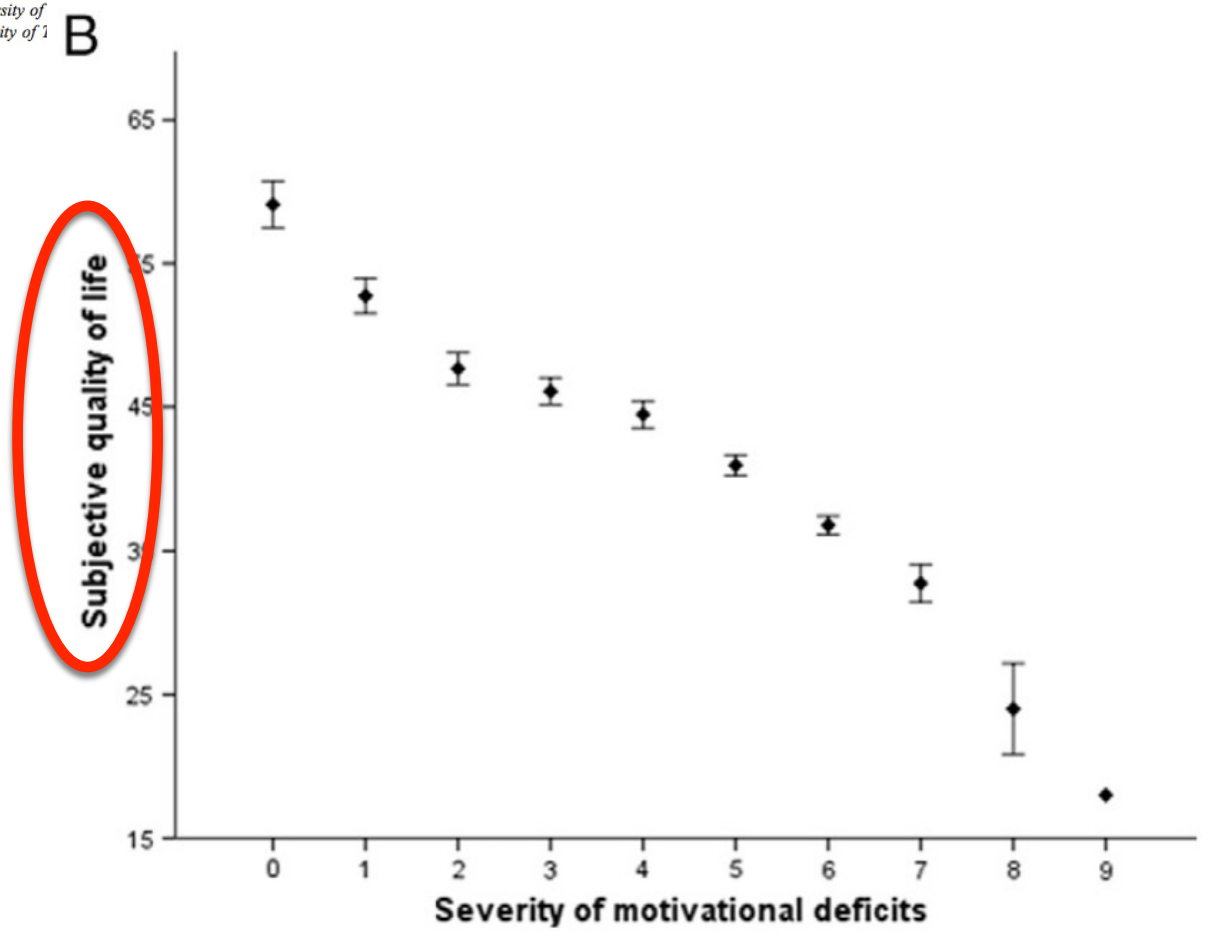




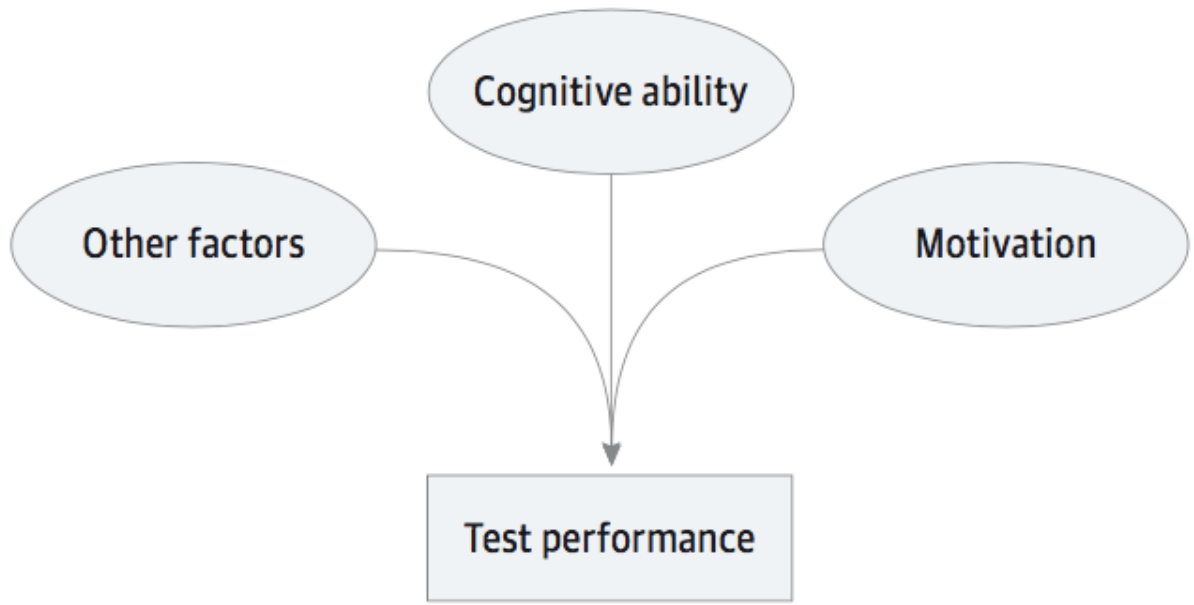
Why is it important ? (2)

Original Investigation

Motivational Deficits and Cognitive Test Performance in Schizophrenia

Gagan Fervaha, BSc; Konstantine K. Zakzanis, PhD; George Foussias, MD, PhD; Ariel Graff-Guerrero, MD, PhD; Ofer Agid, MD; Gary Remington, MD, PhD

Figure 1. Illustration of the Components of Cognitive Test Performance

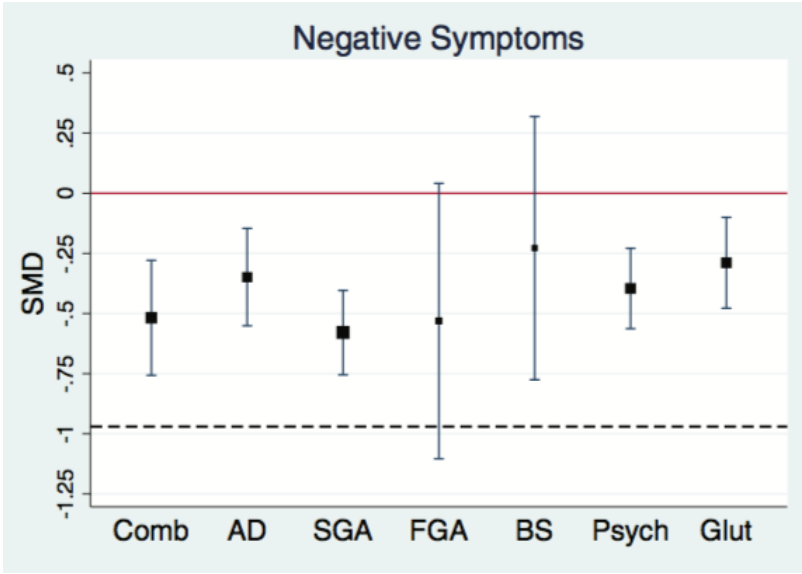


Why is it important ? (3)

Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials

Paolo Fusar-Poli[1,2,6], Evangelos Papanastasiou*[,1,6], Daniel Stahl[3,6], Matteo Rocchetti[1,4], William Carpenter[5], Sukhwinder Shergill[1], and Philip McGuire[1,2]

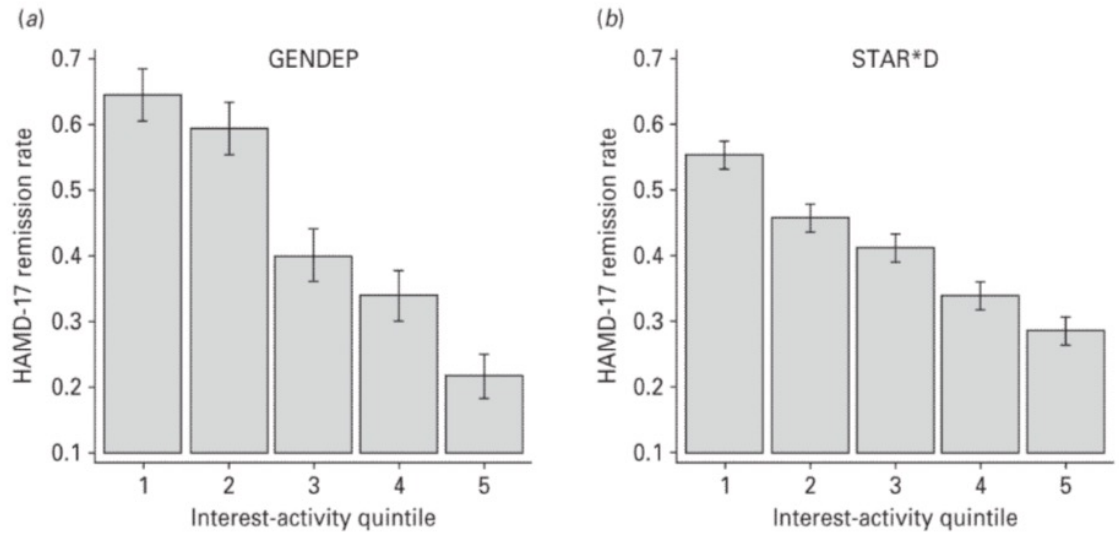
Schizophrenia Bulletin vol. 41 no. 4 pp. 892–899, 2015
doi:10.1093/schbul/sbu170



Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms

R. Uher[1,*], R. H. Perlis[2], N. Henigsberg[3], A. Zobel[4], M. Rietschel[5], O. Mors[6], J. Hauser[7], M. Z. Dernovsek[8], D. Souery[9], M. Bajs[3], W. Maier[4], K. J. Aitchison[1], A. Farmer[1], and P. McGuffin[1]

Psychol Med. 2012 May ; 42(5): 967–980. doi:10.1017/S0033291711001905.



How do we measure motivation ?

How do we measure motivation ?

1. Are you interested in learning new things?	not at all	slightly	some	a lot
2. Does anything interest you?	not at all	slightly	some	a lot
3. Are you concerned about your condition?	not at all	slightly	some	a lot
4. Do you put much efffort into things?	not at all	slightly	some	a lot
5. Are you always looking for something to do?	not at all	slightly	some	a lot
6. Do you have plans and goals for the future?	not at all	slightly	some	a lot
7. Do you have motivation?	not at all	slightly	some	a lot
8. Do you have the energy for daily activities?	not at all	slightly	some	a lot
9. Does someone have to tell you what to do each day?	not at all	slightly	some	a lot
10. Are you indifferent to things?	not at all	slightly	some	a lot
11. Are you unconcerned with many things?	not at all	slightly	some	a lot
12. Do you need a push to get started on things?	not at all	slightly	some	a lot
13. Are you neither happy nor sad, just in between?	not at all	slightly	some	a lot
14. Would you consider yourself apathetic?	not at all	slightly	some	a lot

→ No link with physiology

→ Not translational

How to measure motivation ?

- What's missing:
  - Cognitive (computational) description of motivation

- Objectives
  - To dissect motivation in elementary processes
  - To model these processes
  - To characterize their neural correlates
  - To characterize altered processes in a disease

How to measure motivation ?

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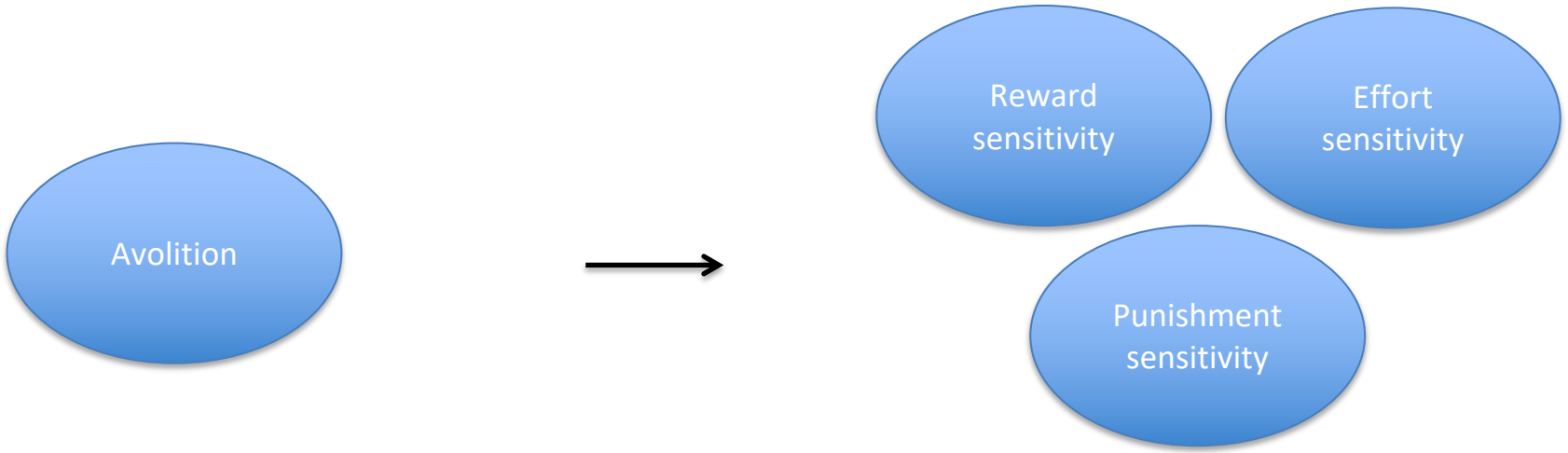
  - Cognitive (computational) description of motivation

- Objectives
  - To dissect motivation in elementary processes
  - To model these processes
  - To characterize their neural correlates
  - To characterize altered processes in a… patient !

How to measure motivation ?

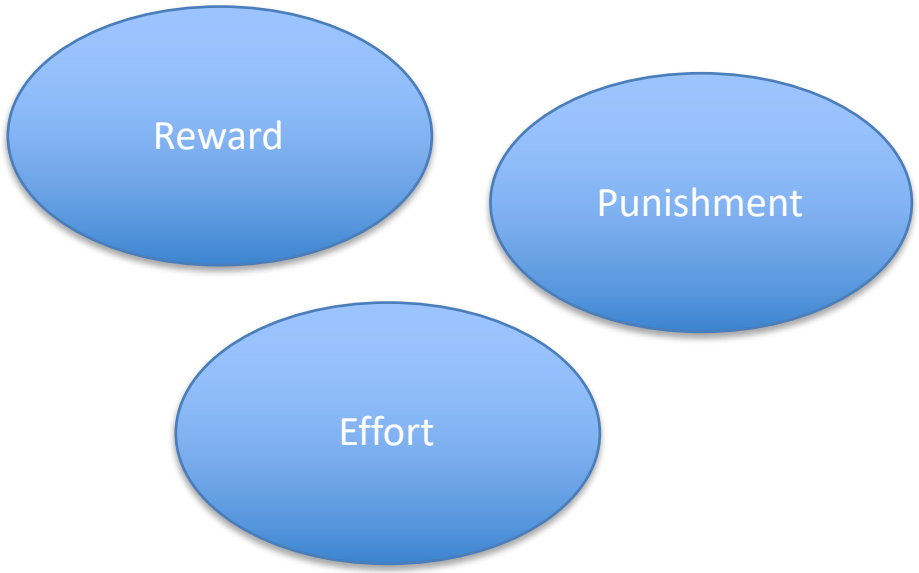


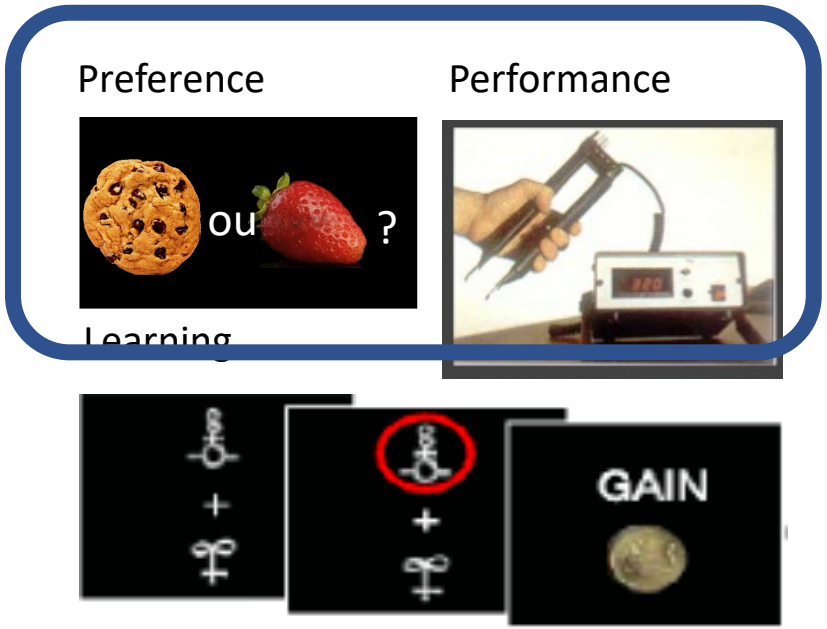
Psychometric scale

Computational phenotyping

A clinical battery for motivation disorders

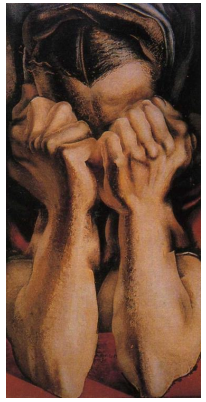
- Sensitivity to 3 dimensions
- In 3 types of behavioural tests
- With computational modelling

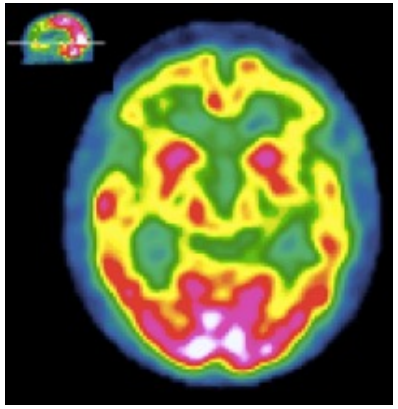


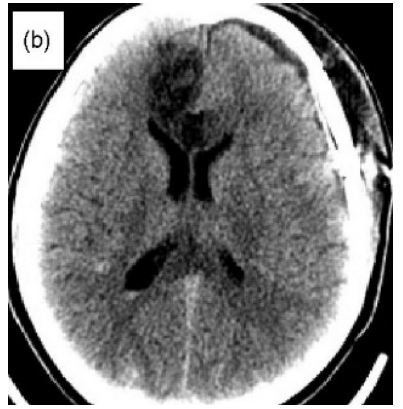


A clinical battery for motivation disorders

- Ongoing studies in neuropsychiatric disorders:
  - Depression / schizophrenia
  - Brain lesions
  - Neurodegenerative diseases (FTD, Parkinson)
  - Neuro-inflammation

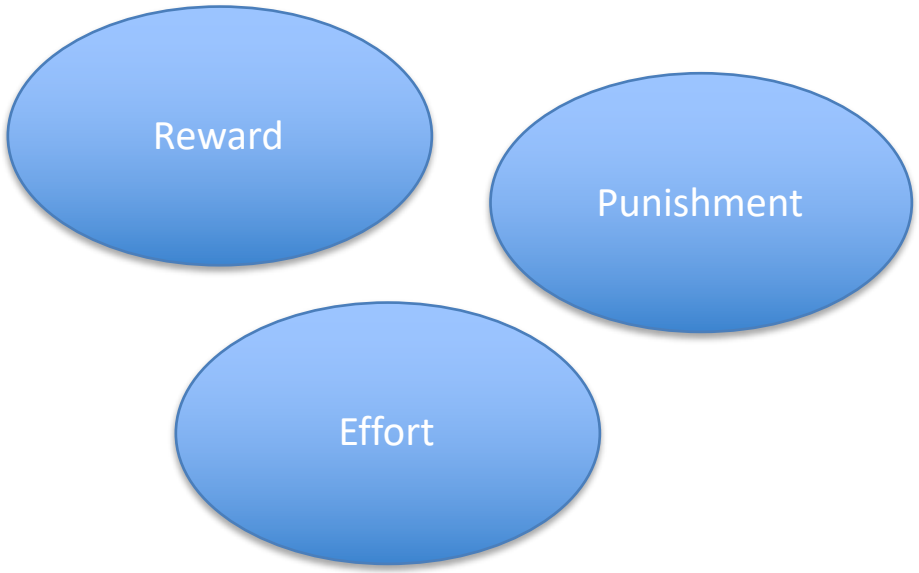




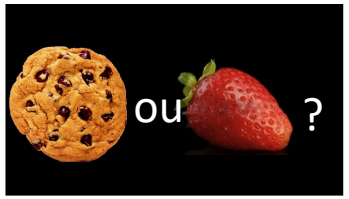


A clinical battery for motivation disorders

- Sensitivity to 3 dimensions
- In 3 types of behavioural tests
- With computational modelling

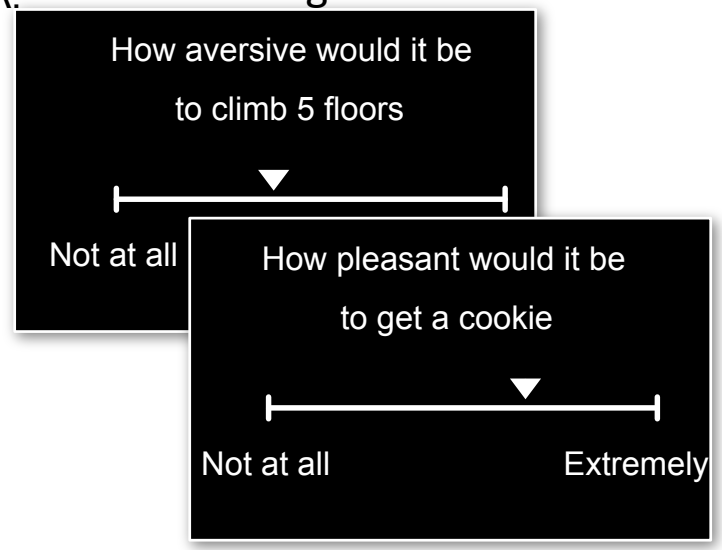


Preference

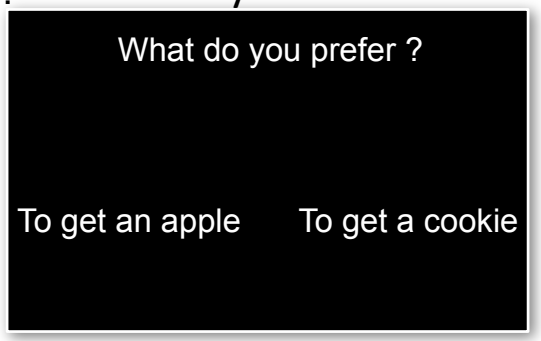


Preference tasks

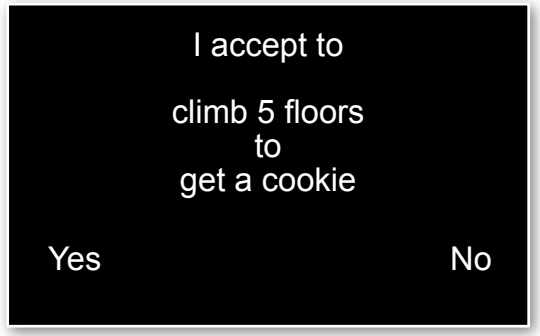
A. Rating



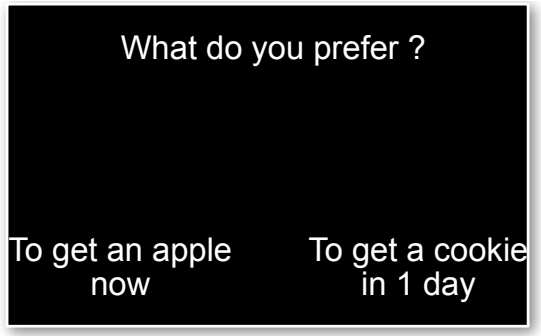
B. Binary choices



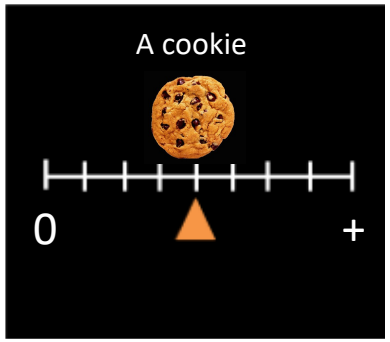
C. Yes/No choices



D. Intertemporal choices



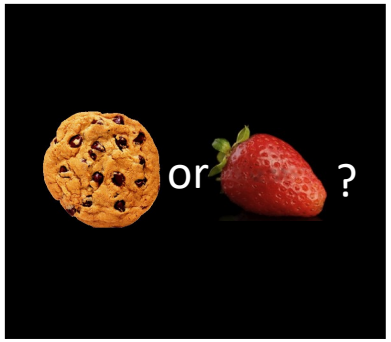
Preference tasks: usual approach



Rating

$$p(choice = A) = \frac{1}{1 + e^{-\beta (R_A - R_B)}}$$

Decision rule



Binary choices

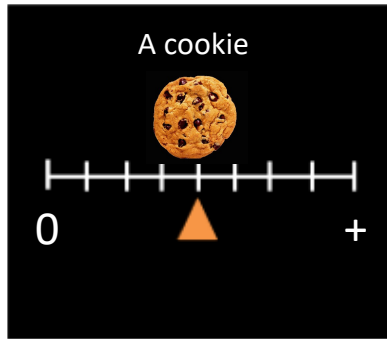
Walk 2 km
To
Get a cookie

Yes / No choice

A cookie tomorrow
or
A marshmallow now

Intertemporal choices

Preference tasks : usual approach



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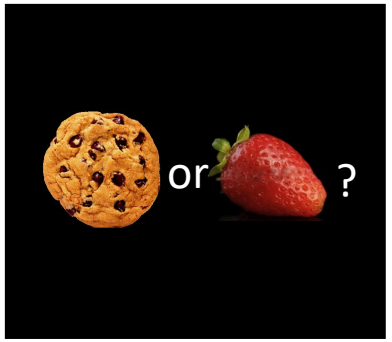


Binary choices

Discounting

$$R' = \frac{R}{1 + \kappa D}$$

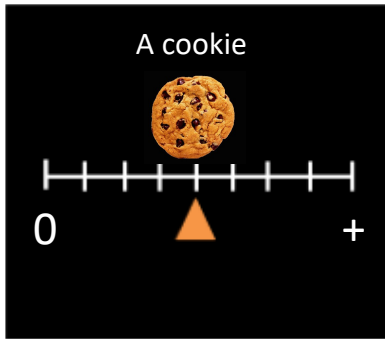
Walk 2 km
To
Get a cookie

Yes / No choice

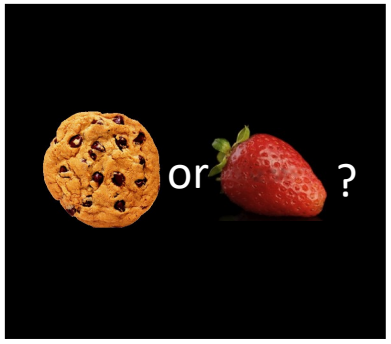
A cookie tomorrow
or
A marshmallow now

Intertemporal choices

Preference tasks : fit all behaviours together



Rating



Binary choices

values

Walk 2 km
To
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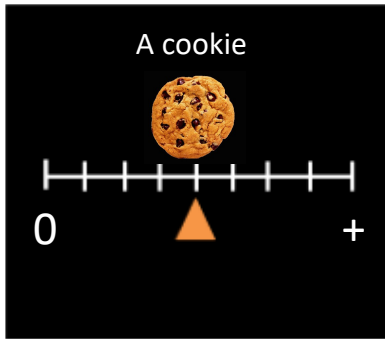
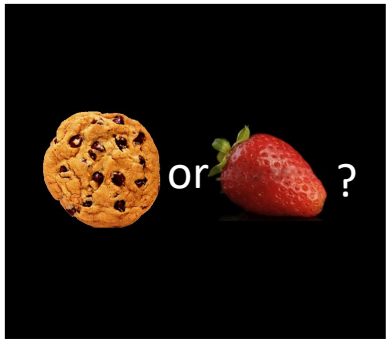
Intertemporal choices

Preference tasks : fit all behaviours together



Rating

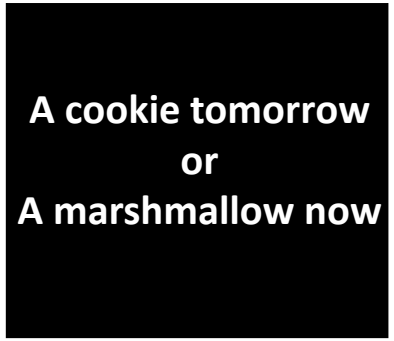


Binary choices

values

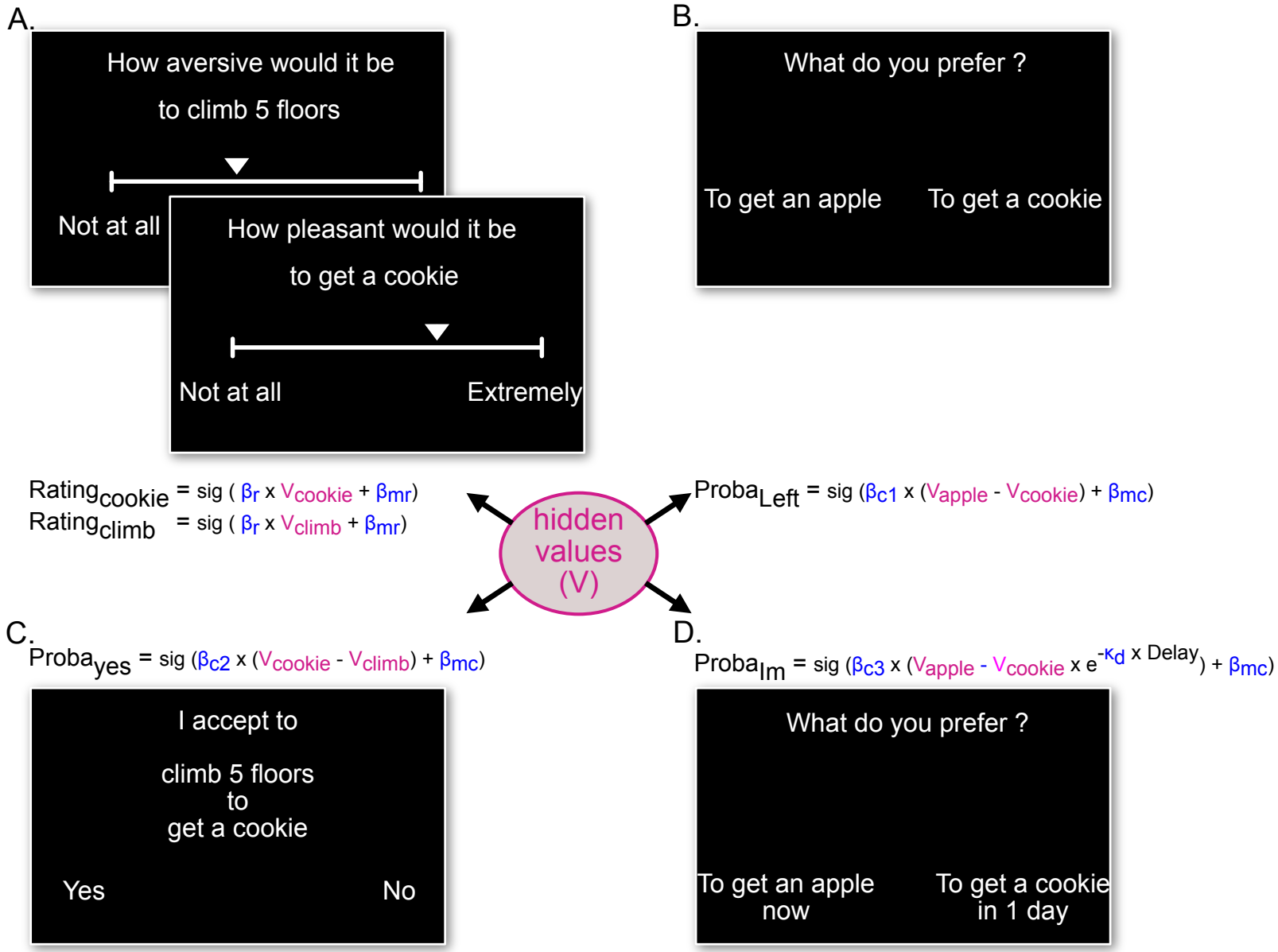
As free parameters

Yes / No choice

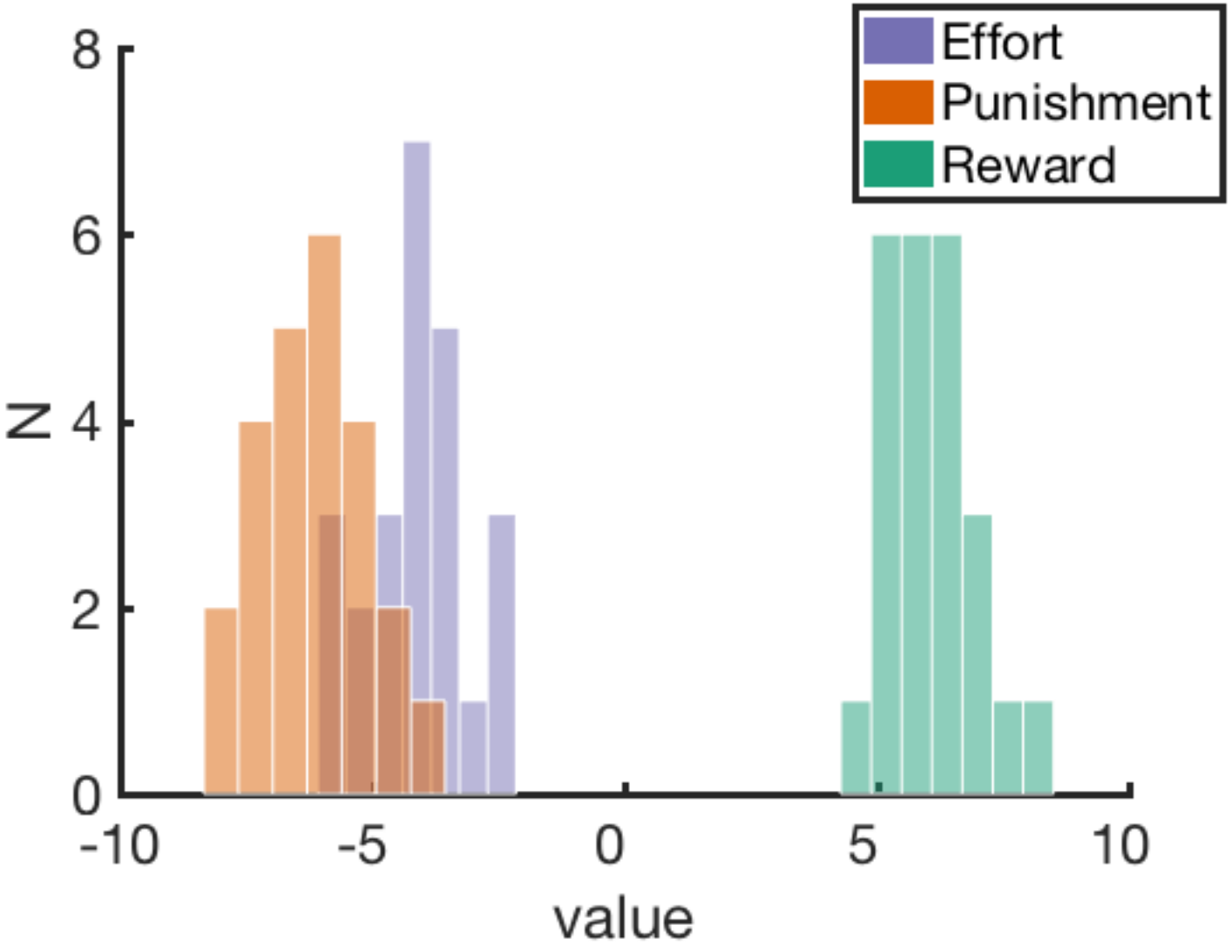


Intertemporal choices

Preference tasks : modelling principles



Preference tasks : modelling principles



+ Task specific parameters
  - Scaling Factors
  - Discount factors…

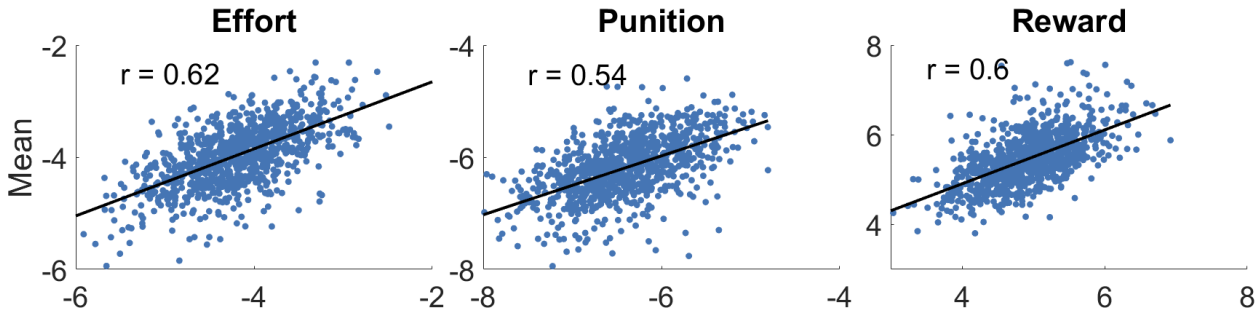
Preference tasks : modelling validation

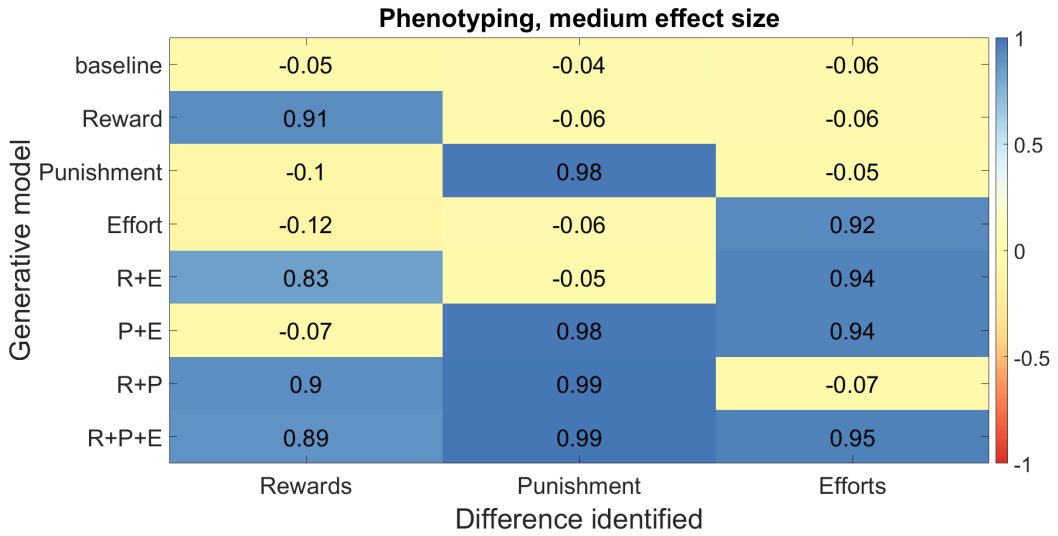
- Simulations

Pablo Carillo

Preference tasks : modelling validation

- Simulations
  - Ability to recover (shift of) hidden values

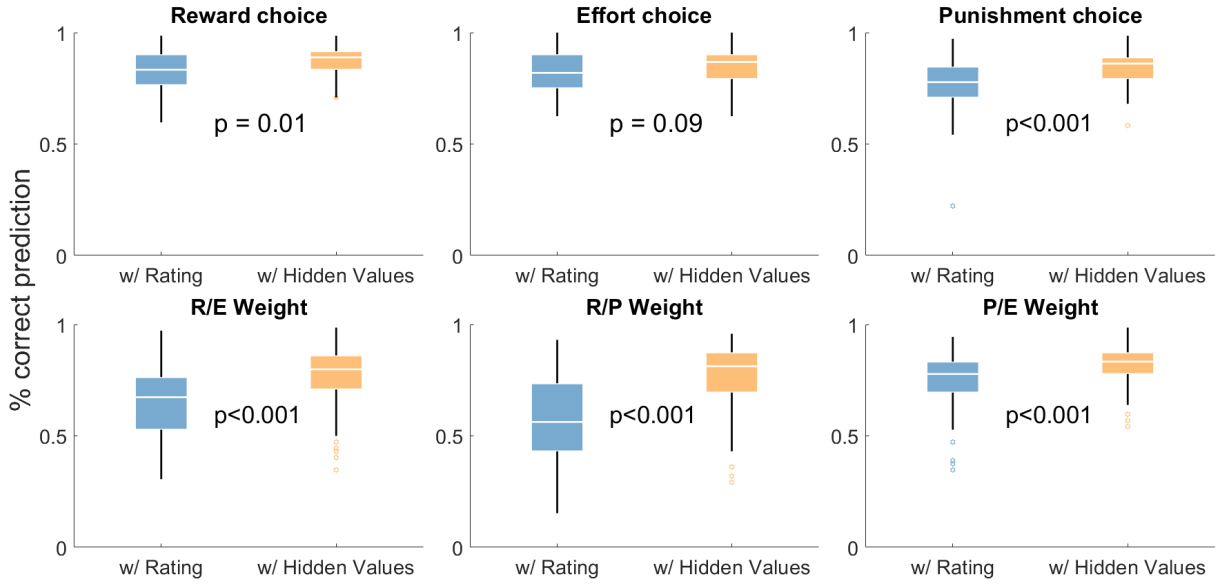




Preference tasks : validation

- Simulations
  - Ability to recover (shift) in hidden values

- Out of sample (leave N out) validation
  - Higher balanced accuracy to predict choices (compared to ratings)



Preference tasks : validation

- Simulations
  - Ability to recover (shift) in hidden values
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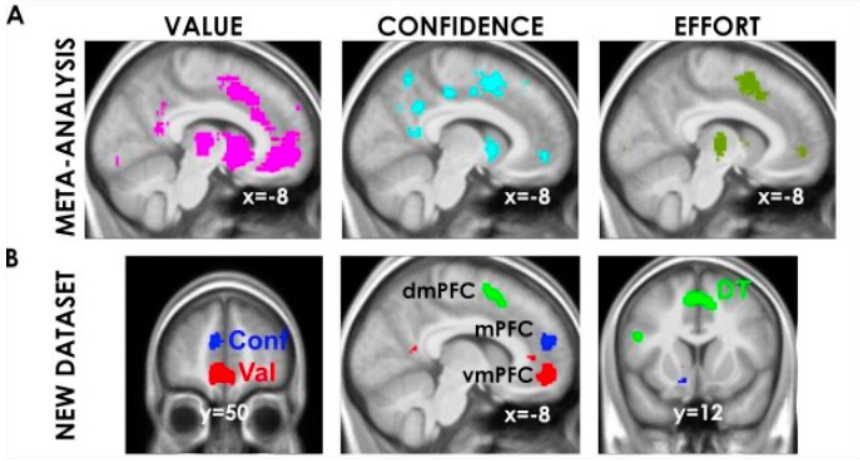
  - Higher balanced accuracy to predict choices (compared to ratings)
- “Brain” validation
  - Not conclusive (for model-based > model-free)

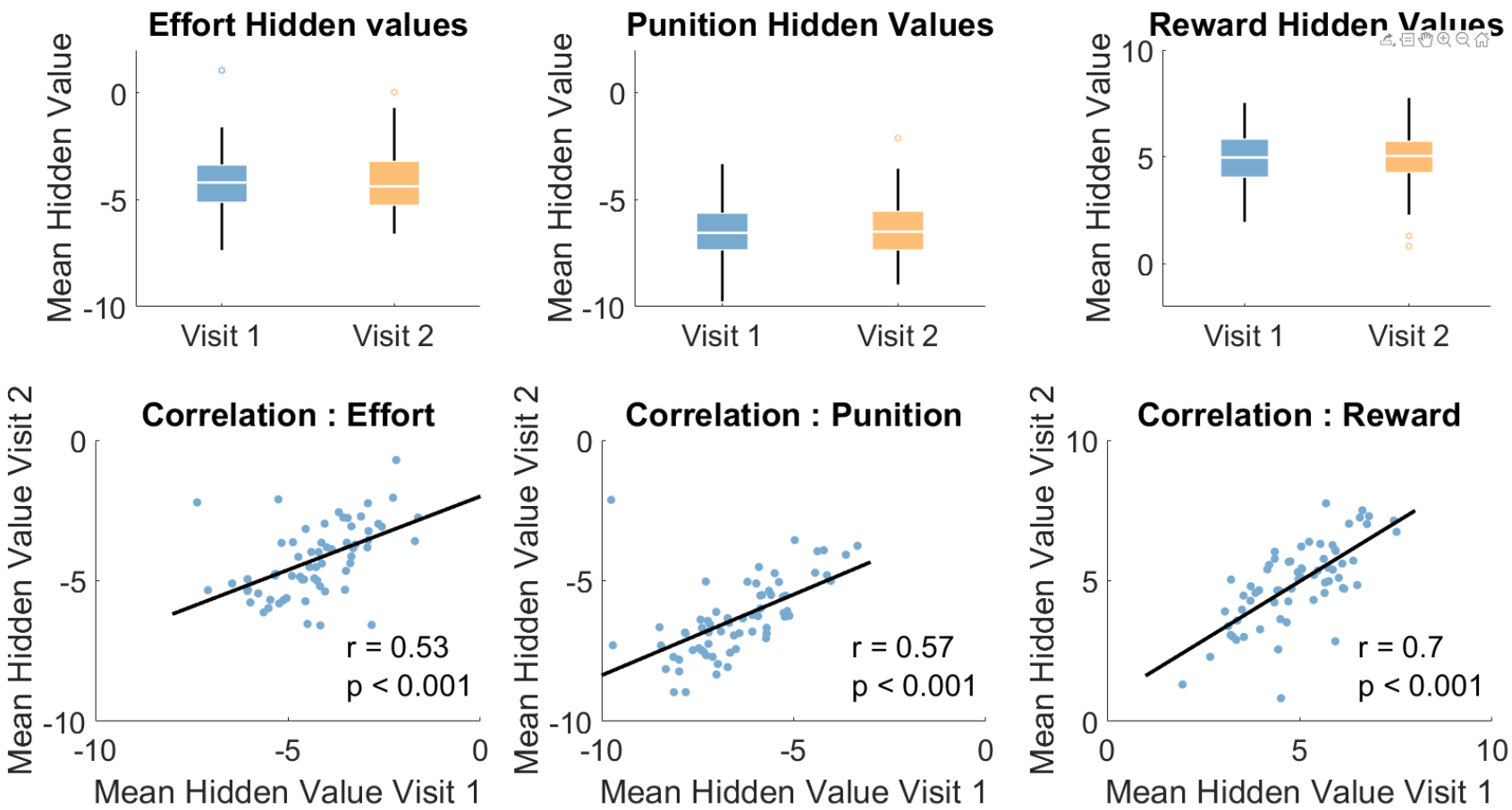


Clairis et. al 2022

Preference tasks : validation

- Simulations
  - Ability to recover (shift) in hidden values
- Out of sample (leave N out) validation
  - Higher balanced accuracy to predict choices (compared to ratings)
- “Brain” validation
  - Not conclusive (for model-based > model-free)
- Test-Retest
  - 72 participants
  - [18 – 69 y]
  - 2 sessions, 4 weeks apart

Claire Jaffré


Effort Hidden values
Mean Hidden Value
0
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Visit 1
Visit 2
Punition Hidden Values
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-10
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Reward Hidden Values
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Visit 1
Visit 2
Correlation : Effort
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0
-5
-10
r = 0.53
p < 0.001
-10
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Mean Hidden Value Visit 1
Correlation : Punition
Mean Hidden Value Visit 2
0
-5
-10
r = 0.57
p < 0.001
-10
-5
0
Mean Hidden Value Visit 1
Correlation : Reward
Mean Hidden Value Visit 2
10
5
0
r = 0.7
p < 0.001
0
5
10
Mean Hidden Value Visit 1

Comparison of populations

ELSEVIER

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

Available online 8 August 2022

In Press, Journal Pre-proof ⓘ

Archival Report

Elevated effort cost identified by computational modeling as a distinctive feature explaining multiple behaviors in patients with depression

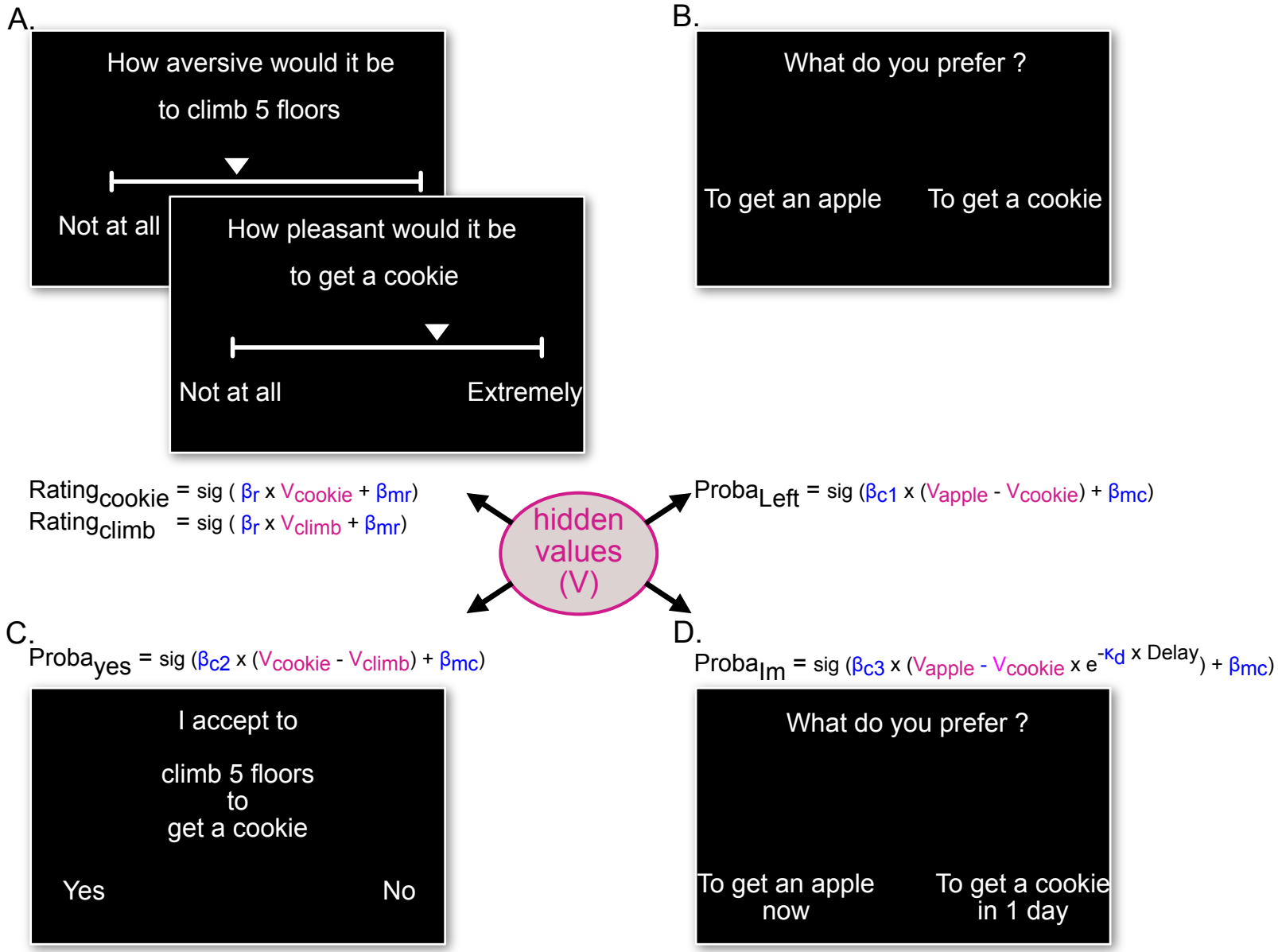
Fabien Vinckier MD-PhD [1, 2, 3] ✉, Claire Jaffre [1, 2, 3], Claire Gauthier MD [2, 3], Sarah Smajda MD [2, 3], Pierre Abdel-Ahad MD [2, 3], Raphaël Le Bouc MD-PhD [1, 4, 5], Jean Daunizeau PhD [1, 6], Mylène Fefeu MD [2, 3], Nicolas Borderies PhD [1], Marion Plaze MD-PhD [2, 3], Raphaël Gaillard MD-PhD [2, 3, 7, #], Mathias Pessiglione PhD [1, 6, #]

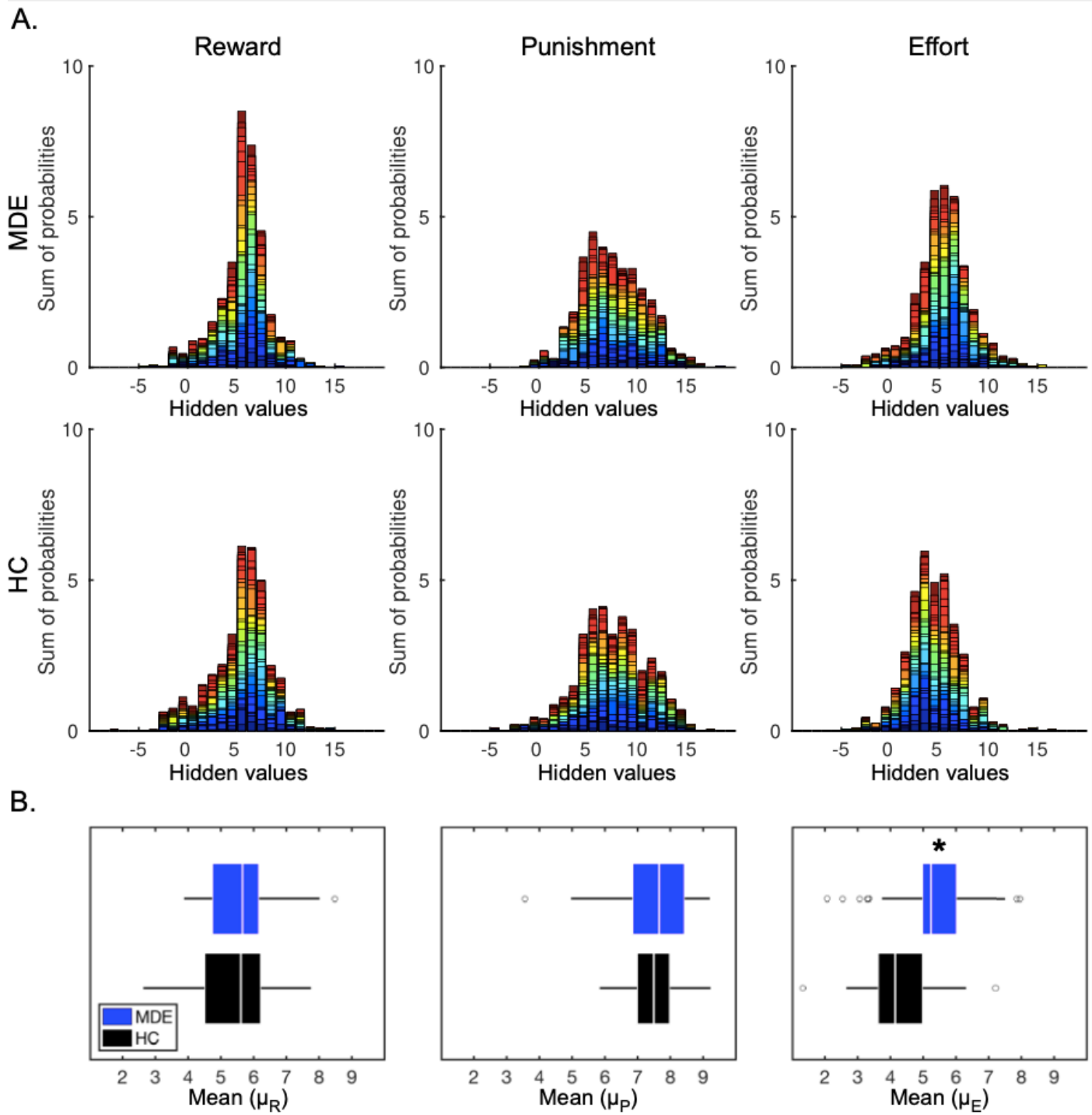
Comparison of populations

	MDE (N = 35)	HC (N = 35)	p-value
Gender (F / M)	18 / 17	18 / 17	1
Age (years)	42.5 (16.9)	43 (16.3)	.902
Education (years)	15.2 (3.8)	15.1 (2.5)	.881
Currently active* (N)	21	31	.116
PCSA (cm^2)	43.0 (10.6)	43.2 (10.0)	.929
MADRS (depression)	36.1 (7.4)	2.9 (2.8)	< 0.001
Starkstein (apathy)	23.8 (5.6)	7.4 (4.0)	< 0.001
SHAPS (anhedonia)	5.4 (4.3)	0.5 (1.0)	< 0.001
Thase & Rush staging	6 / 15 / 9 / 5	NA	

	MDD (N = 20)	Bipolar disorder (N = 15)	p-value
Gender (F / M)	11 / 9	7 / 8	0.625
Age (years)	45.7 (19.0)	38.1 (12.9)	0.192
Education (years)	14.8 (4.1)	15.8 (3.2)	0.444
Currently active* (N)	11	9	0.767
MADRS (depression)	37.2 (6.9)	34.7 (8.1)	0.333
Starkstein (apathy)	23.7 (6.3)	24.0 (4.7)	0.858
SHAPS (anhedonia)	5.6 (4.7)	5.1 (3.8)	0.723
Thase & Rush staging	2 / 7 / 6 / 5	4 / 8 / 3 / 0	0.104
Lithium (N)	0	6	0.002
Antidepressant (N)	20	4	< 0.001
Atypical antipsychotic (N)	5	10	0.013
Anxiolytic (N)	9	8	0.625

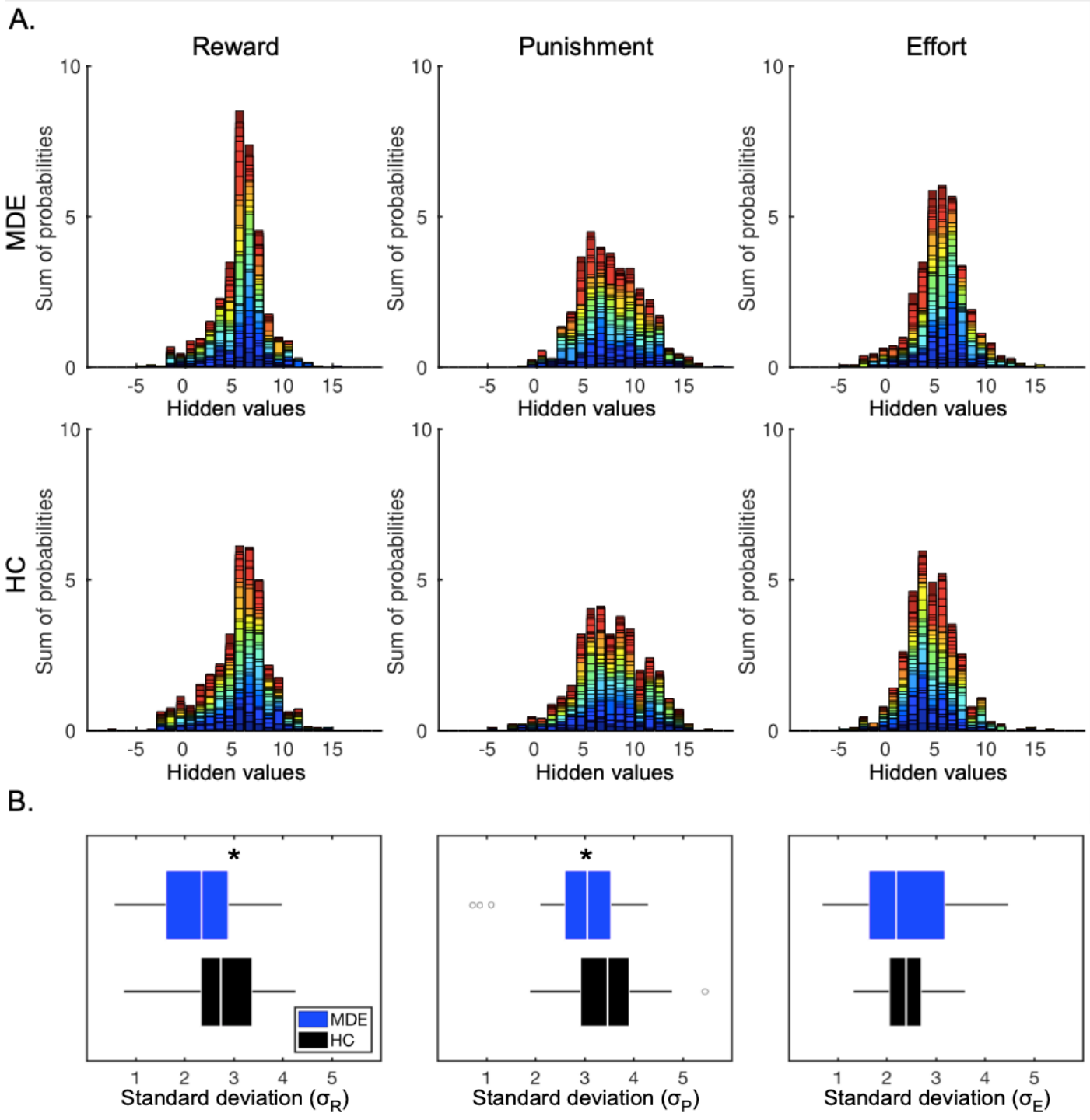
Preference tasks : modelling principles



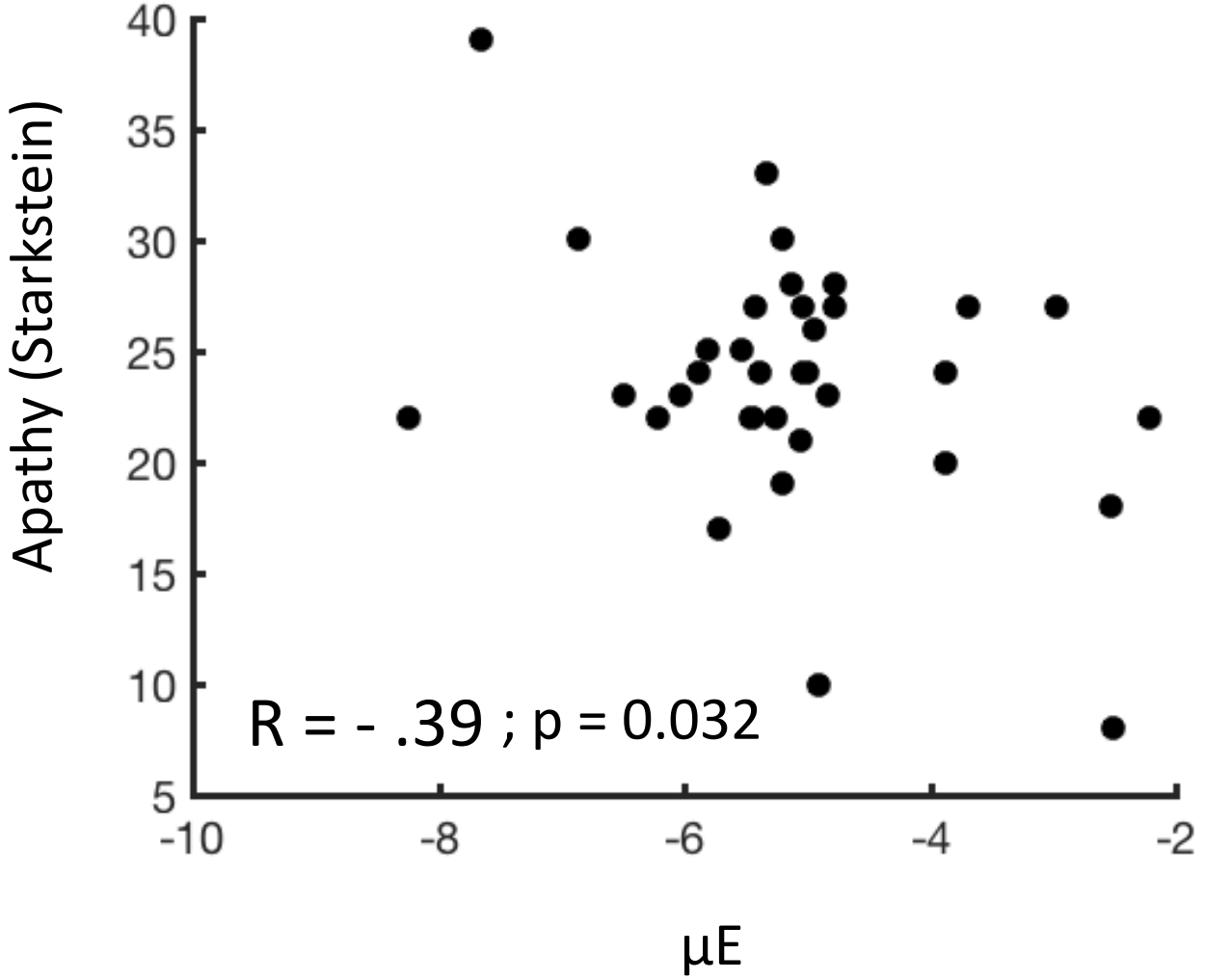

A.
Reward
Punishment
Effort
MDE
HC
Sum of probabilities
Hidden values
B.
MDE
HC
Mean (μ_R)
Mean (μ_P)
Mean (μ_E)
*

Mean

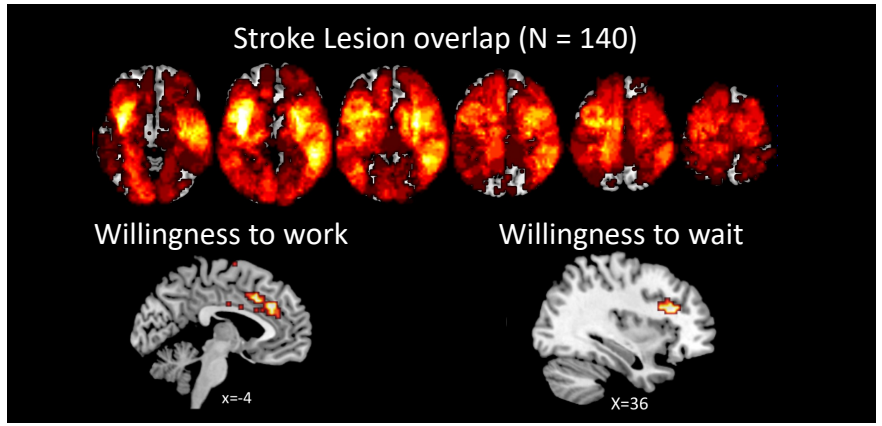
For the record
(standard deviation)

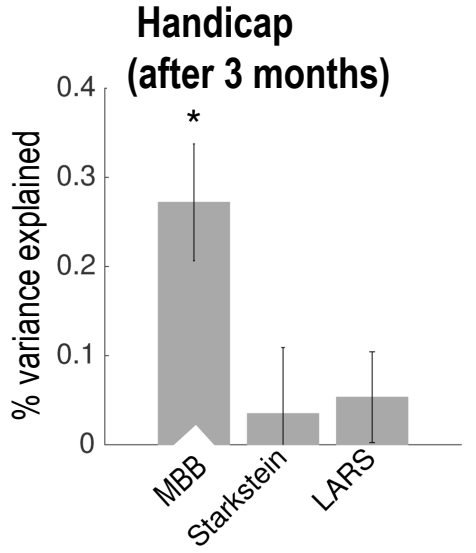


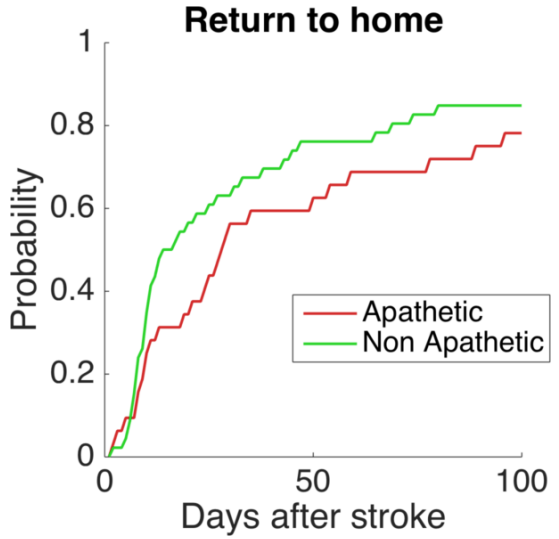
Correlation with clinical scores (just because someone will ask!)



In stroke





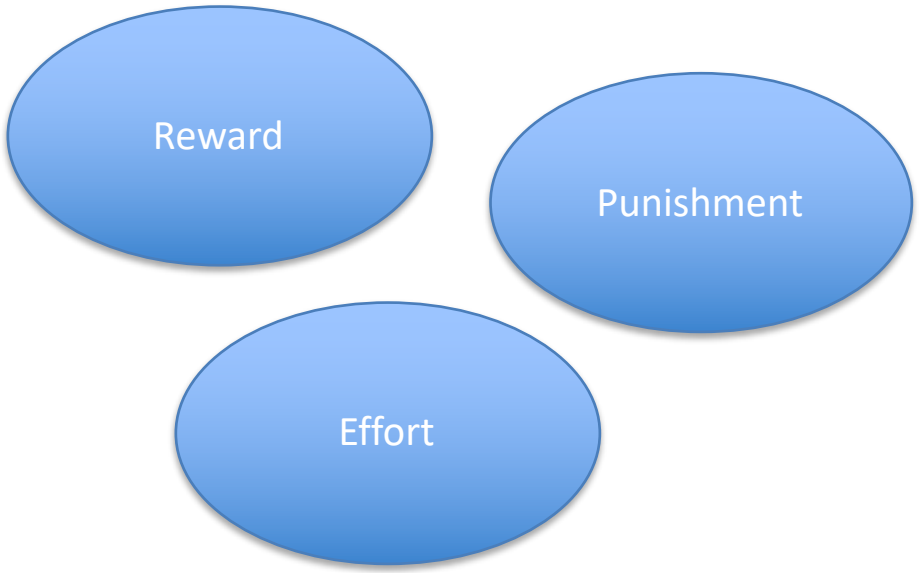


- Short version of the preference tasks
- Computational phenotypes predict when patients will be able to return home

Lebouc et al, in prep

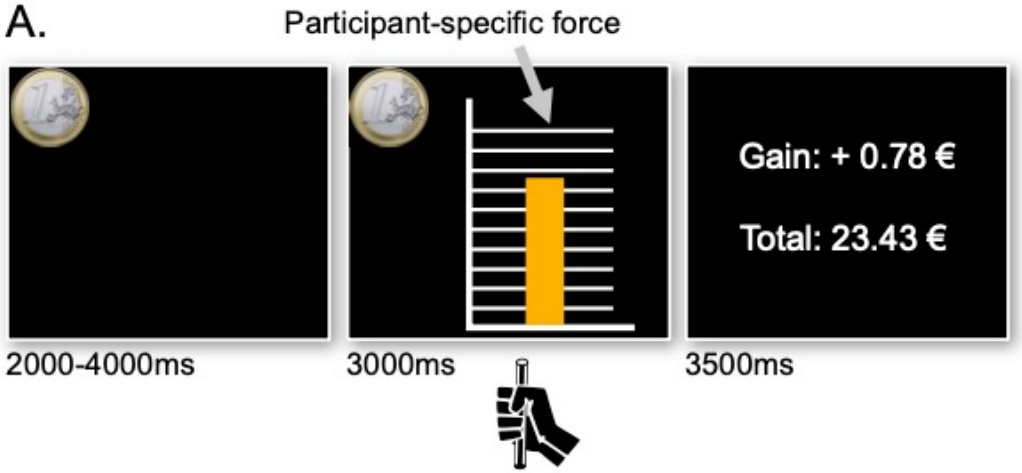
A clinical battery for motivation disorders

- Sensitivity to 3 dimensions
- In 3 types of behavioural tests
- With computational modelling



Performance

Performance tasks



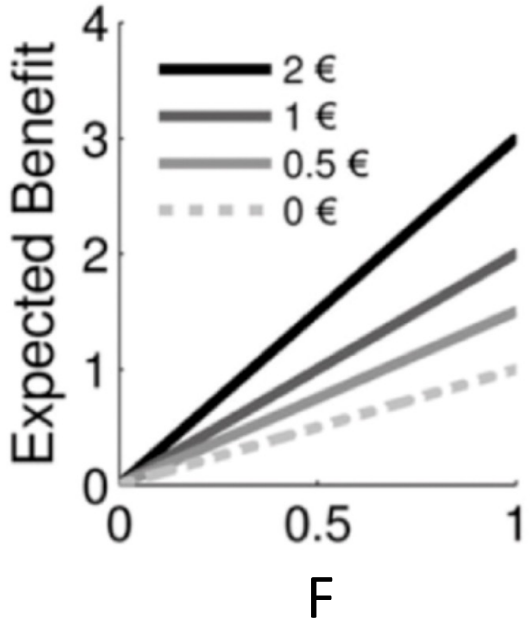
- Payoff is proportional to the performance and to the reward level :

Performance tasks : cost benefit trade-off modelling

Le Bouc, Rigoux et al, 2016 ; Pessiglione et al, 2017

Performance tasks : cost benefit trade-off modelling

$$benefit = K_r RF$$

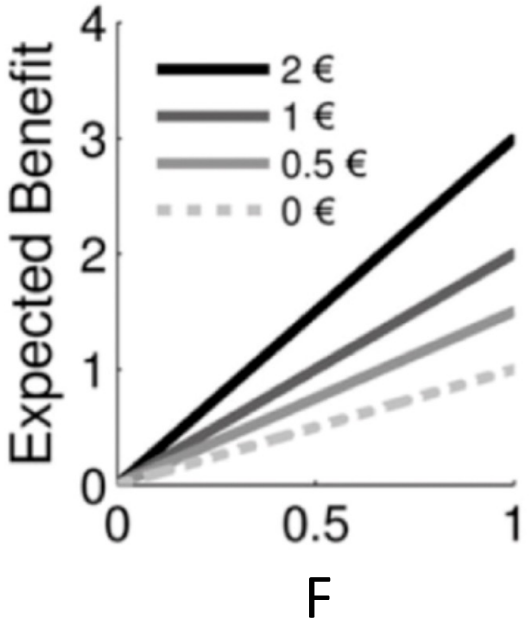


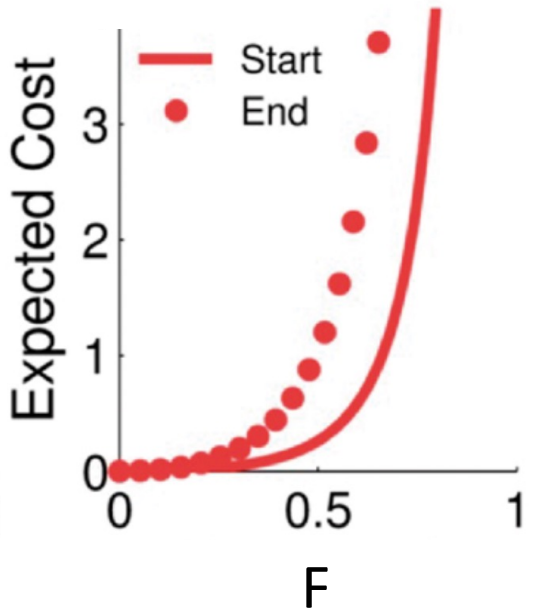
Le Bouc, Rigoux et al, 2016 ; Pessiglione et al, 2017

Performance tasks : cost benefit trade-off modelling

$$benefit = K_r RF$$

$$cost = K_c (1 + K_F N) * (\frac{F}{1-F})^2$$





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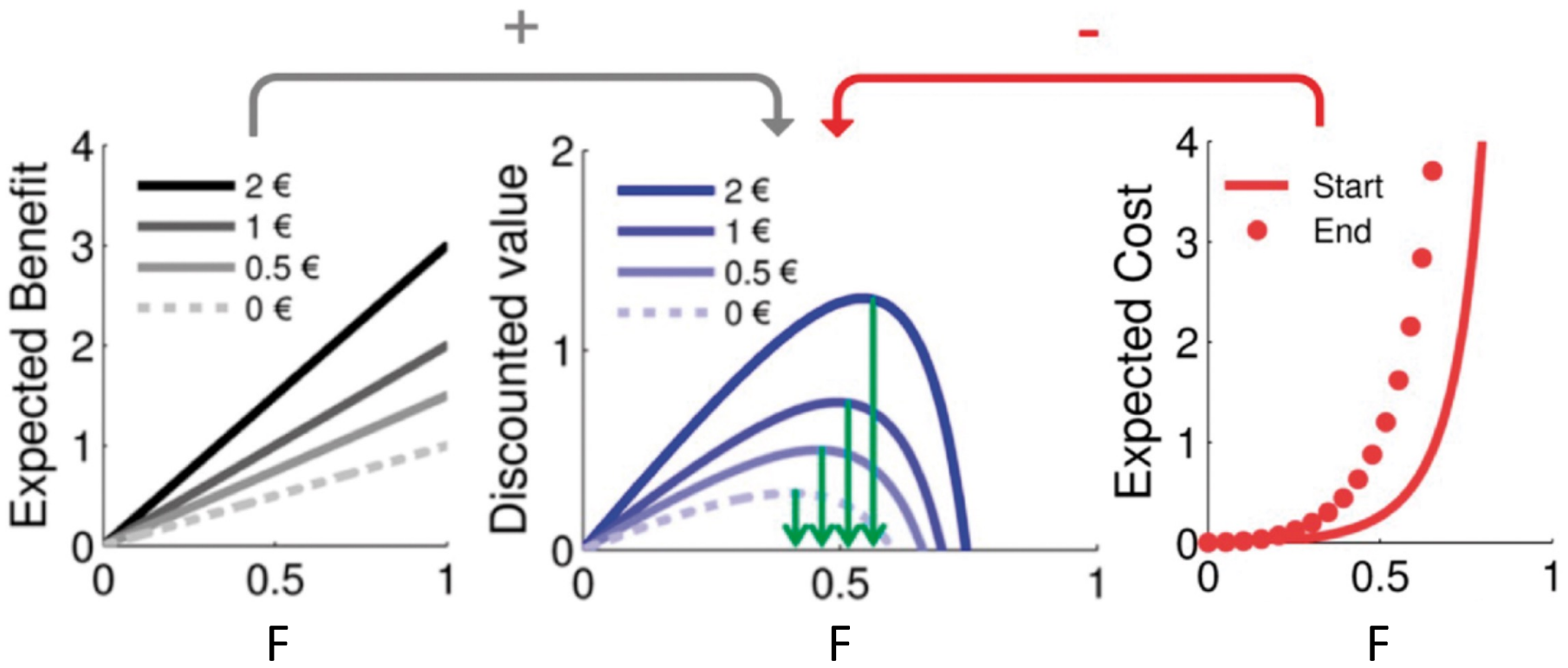
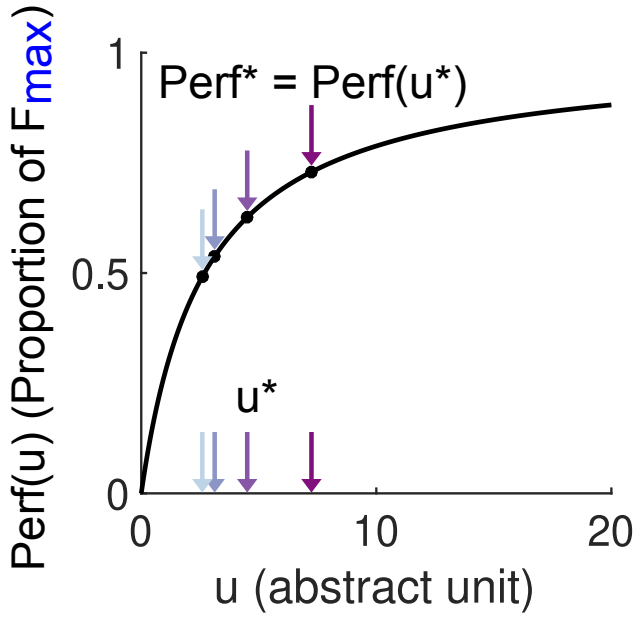


Le Bouc, Rigoux et al, 2016 ; Pessiglione et al, 2017

Performance tasks : cost benefit trade-off modelling

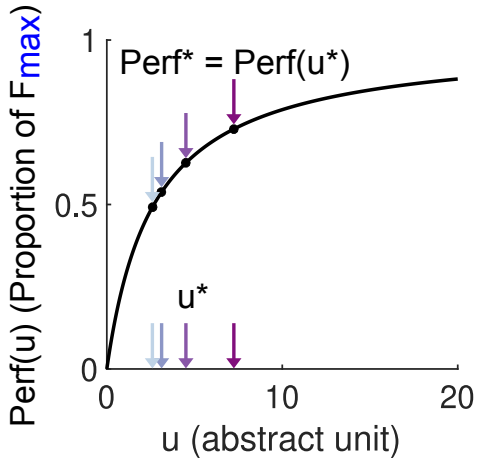
C.



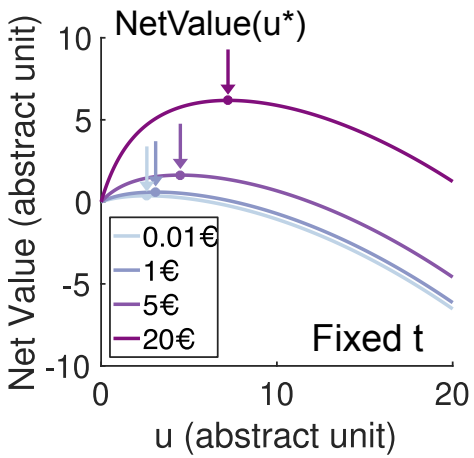
- Resource ≠ performance
- Rewriting to express performance (e.g. force)
  as a function of a resource (e.g. neural drive)

Performance tasks : cost benefit trade-off modelling

C.



$$Perf(u) = \frac{u}{u + T}$$



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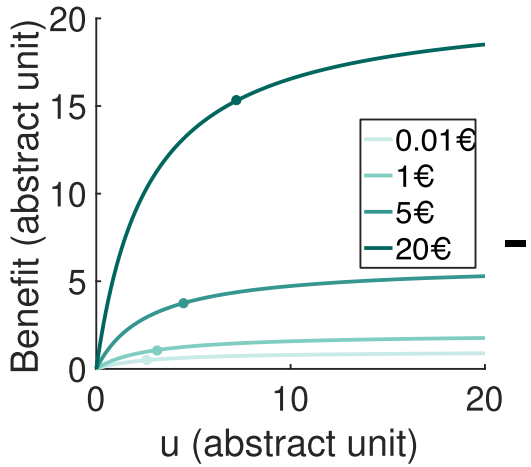

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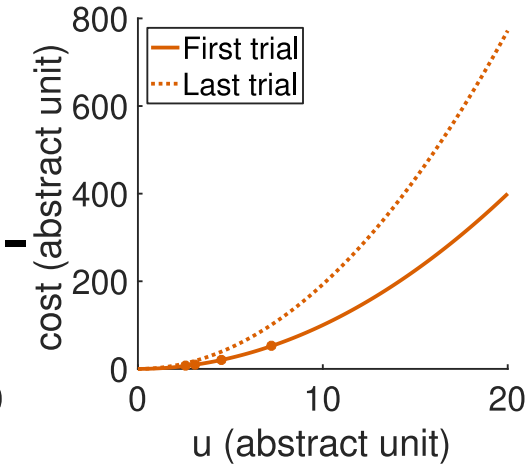


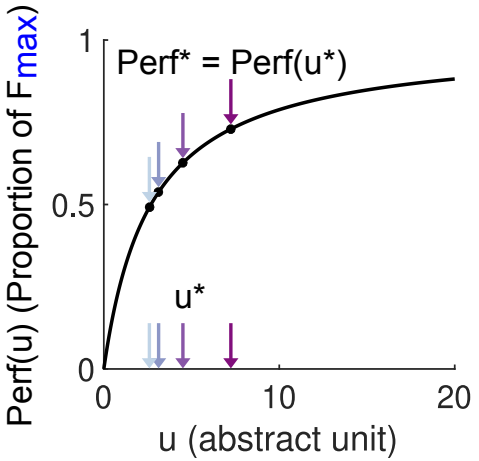
$$NetValue(u,t) = \frac{Perf(u)}{P_{max}} + K_i \times \frac{Perf(u)}{P_{cal}} \times Inc(t) - K_c \times \left(1 + K_f \times \frac{t}{N_t}\right) \times u^2$$

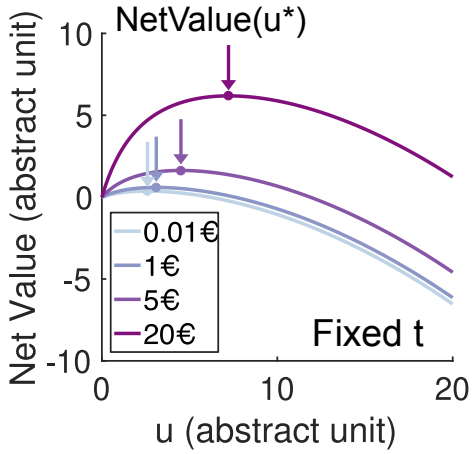
$$Perf^* = Perf(u^*) = Perf(\underset{u}{argmax}\ (NetValue))$$

Vinckier et al. 2022

Performance tasks : cost benefit trade-off modelling

C.





$$Perf(u) = \frac{u}{u + T}$$

$$NetValue(u,t) = \frac{Perf(u)}{P_{max}} + K_i \times \frac{Perf(u)}{P_{cal}} \times Inc(t) - K_C \times (1 + K_f \times \frac{t}{N_t}) \times u^2$$

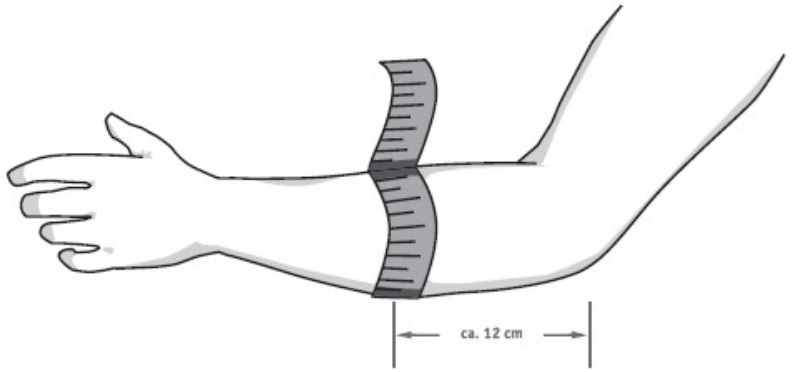
$$Perf^* = Perf(u^*) = Perf(\underset{u}{argmax}(NetValue))$$

« Hidden » free parameter !

Pmax = theoretical maximal performance

Vinckier et al. 2022

Theoretical Pmax (based on morphometric measures for motor effort)



Performance tasks : modelling validation

- Simulations
  - Ability to recover free parameters (sensitivity to reward, effort, fatigue)
  - Depending on Pmax strategy (fitted or not, accurate prior or not)

Pablo Carillo

Performance tasks : modelling validation

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  - Ability to recover free parameters (sensitivity to reward, effort, fatigue)
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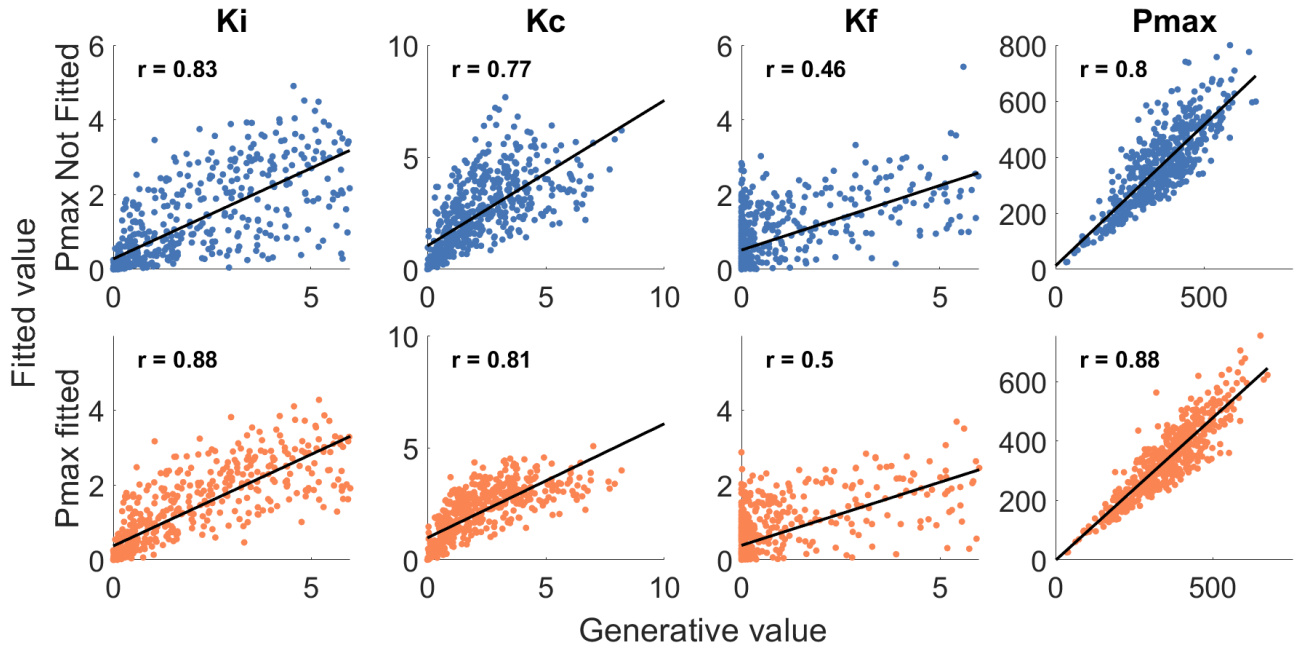

Pablo Carillo

Performance tasks : modelling validation

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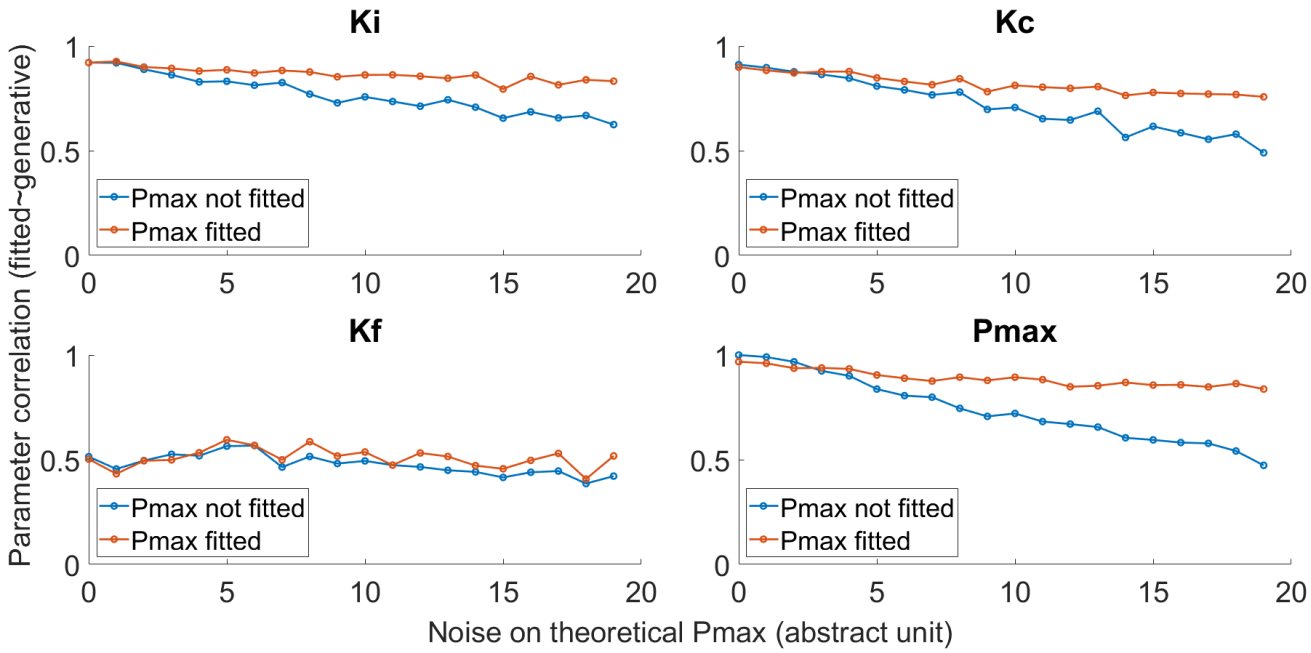
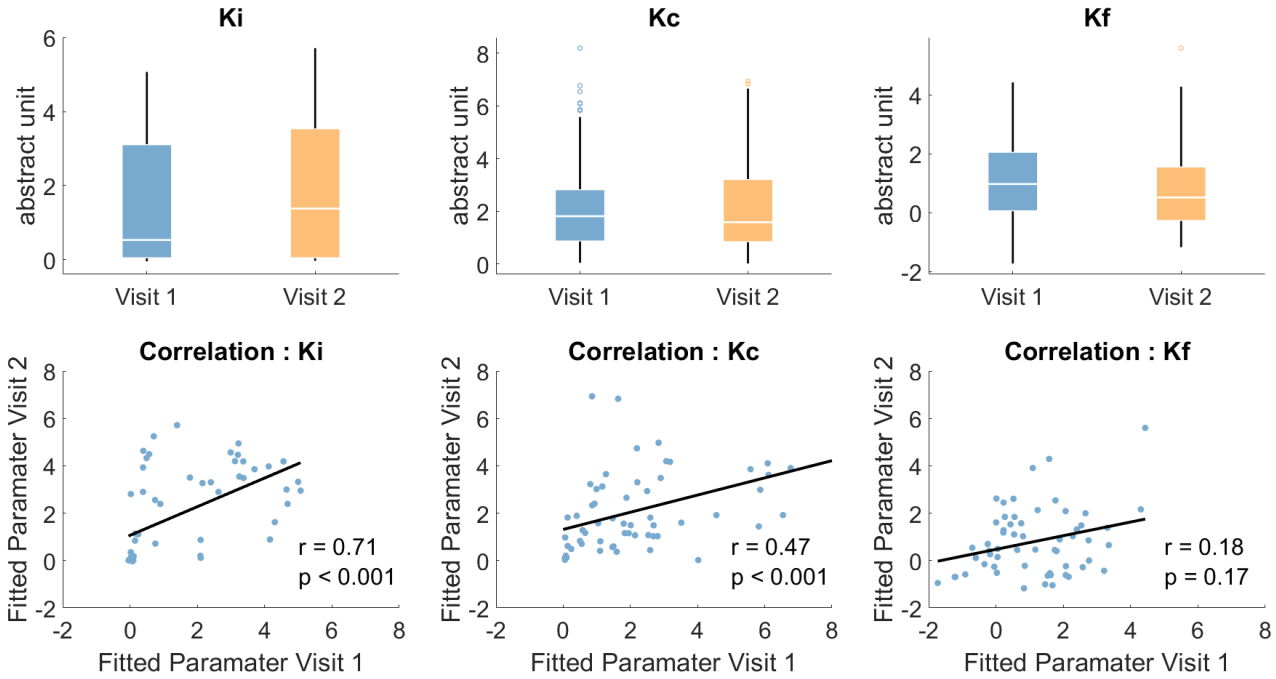


Pablo Carillo

Performance tasks : modelling validation

- Simulations
  - Ability to recover free parameters (sensitivity to reward, effort, fatigue)
  - Depending on Pmax strategy (fitted or not, accurate prior or not)

- Test - Retest



Claire Jaffré

Comparison of populations

ELSEVIER

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

Available online 8 August 2022

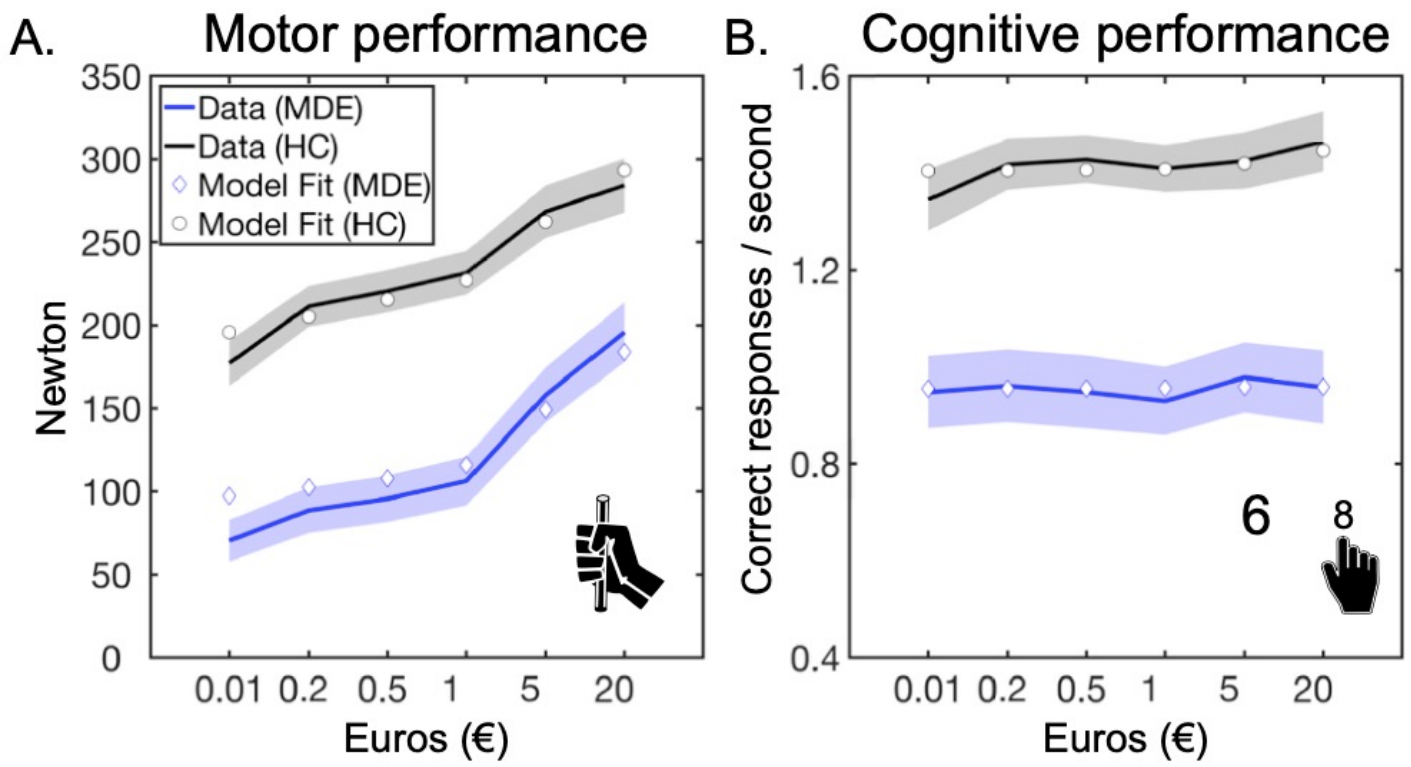
In Press, Journal Pre-proof ⓘ

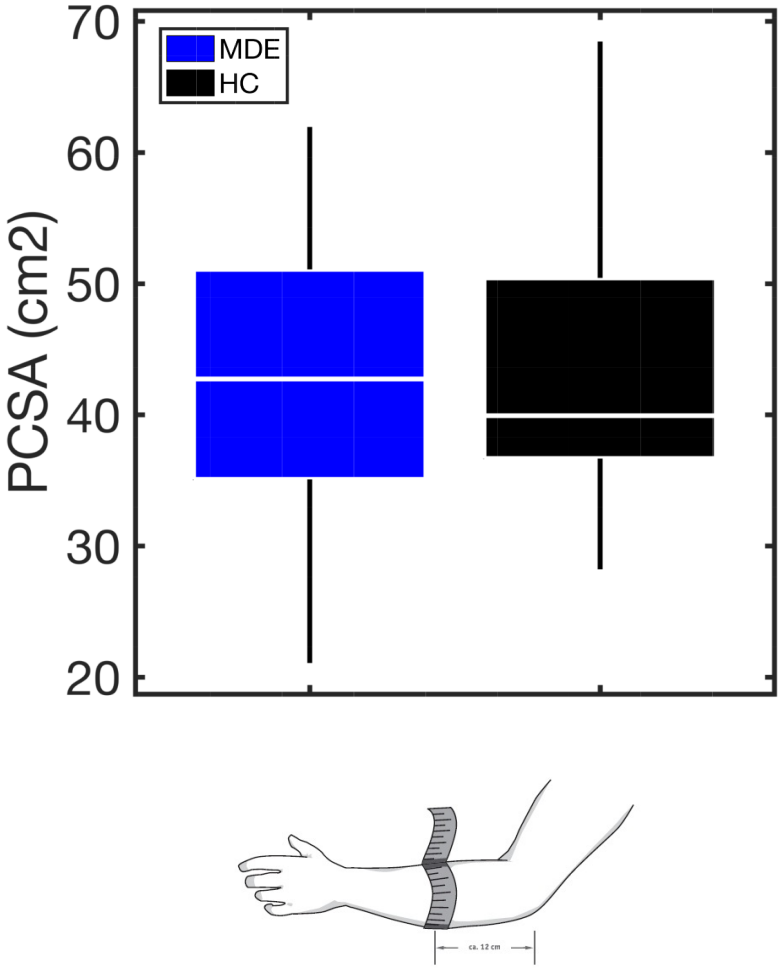
Archival Report

Elevated effort cost identified by computational modeling as a distinctive feature explaining multiple behaviors in patients with depression

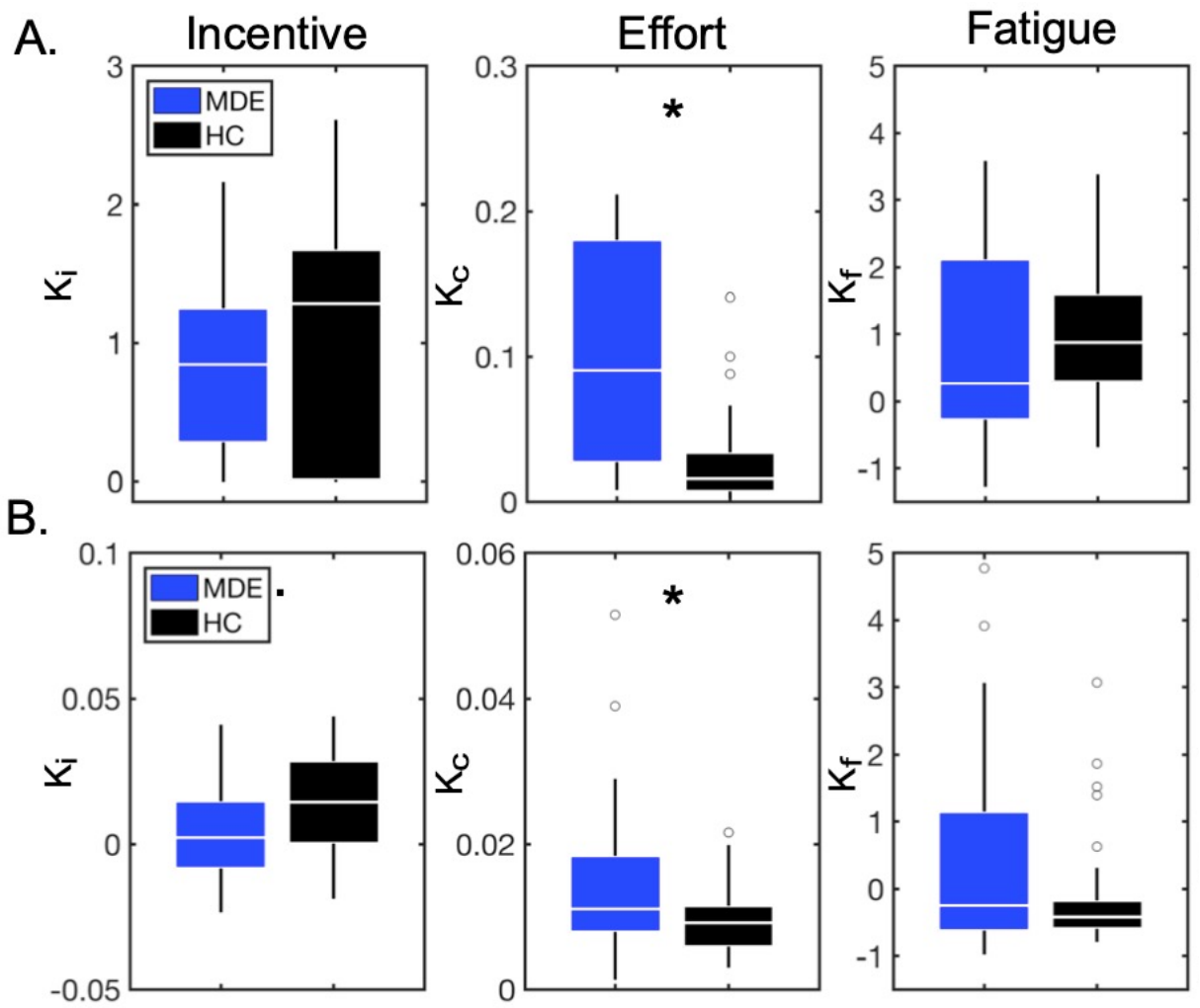
Fabien Vinckier MD-PhD [1, 2, 3] ✉, Claire Jaffre [1, 2, 3], Claire Gauthier MD [2, 3], Sarah Smajda MD [2, 3], Pierre Abdel-Ahad MD [2, 3], Raphaël Le Bouc MD-PhD [1, 4, 5], Jean Daunizeau PhD [1, 6], Mylène Fefeu MD [2, 3], Nicolas Borderies PhD [1], Marion Plaze MD-PhD [2, 3], Raphaël Gaillard MD-PhD [2, 3, 7, #], Mathias Pessiglione PhD [1, 6, #]

Comparison of populations

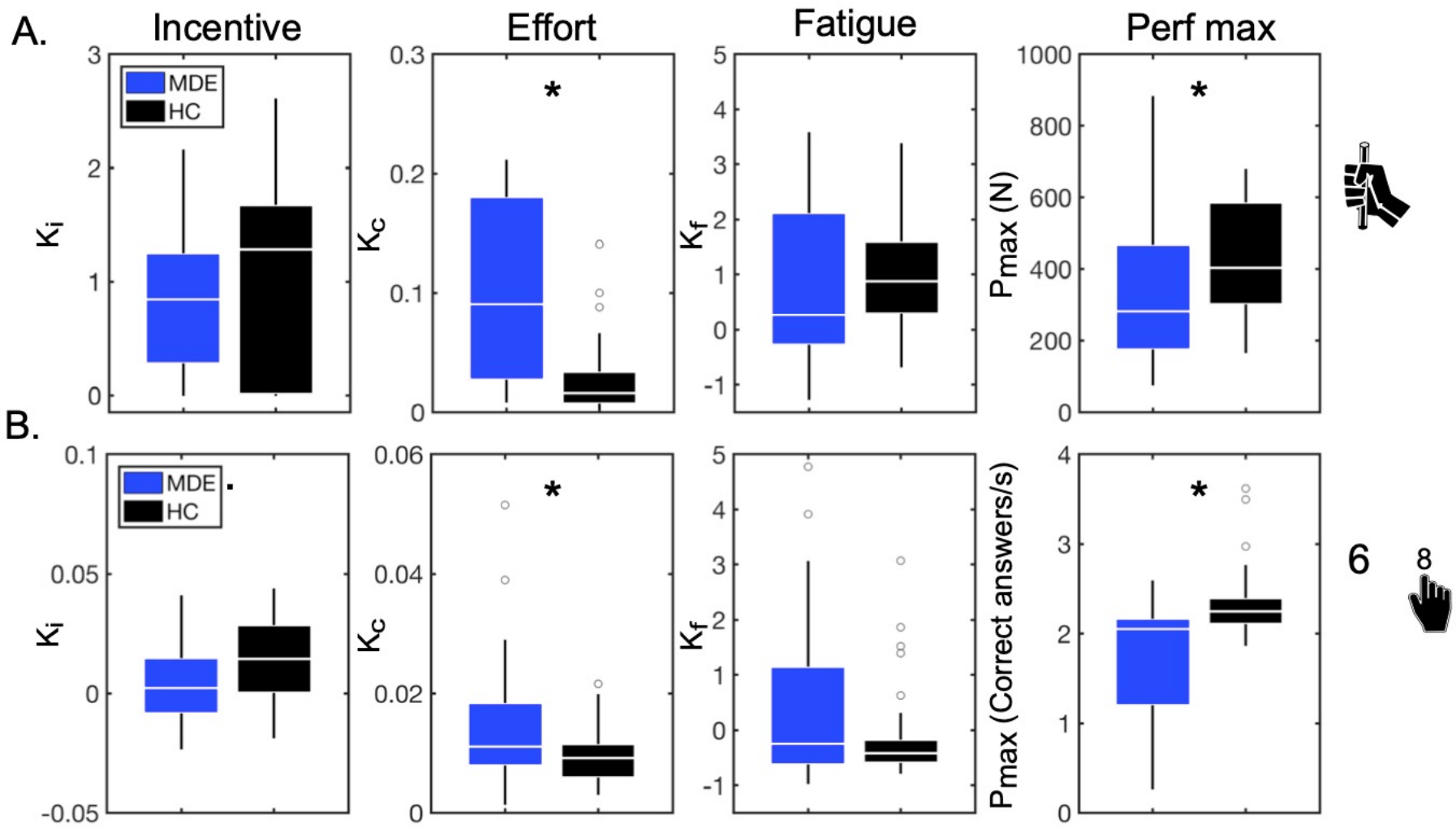




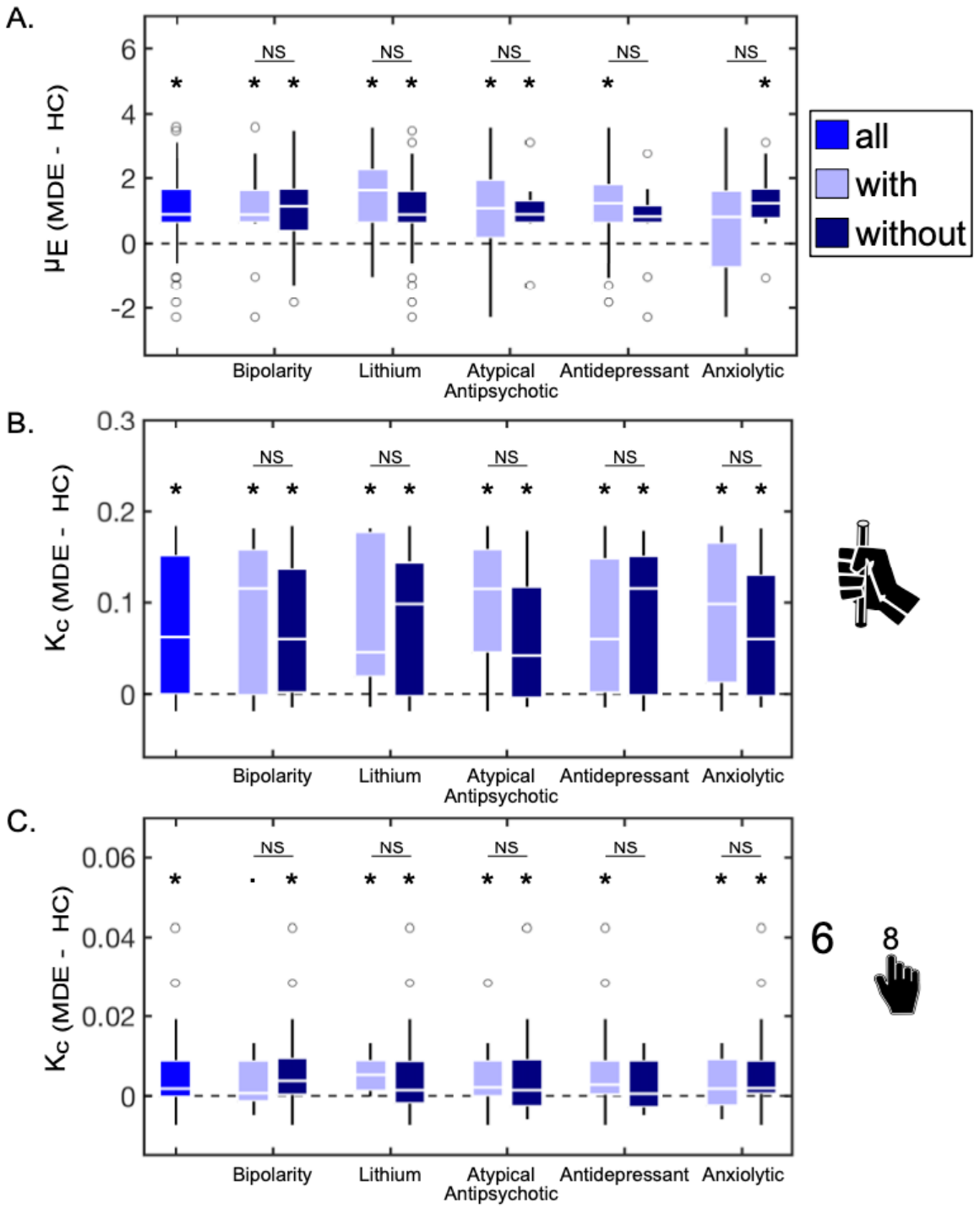
Comparison of populations



Comparison of populations



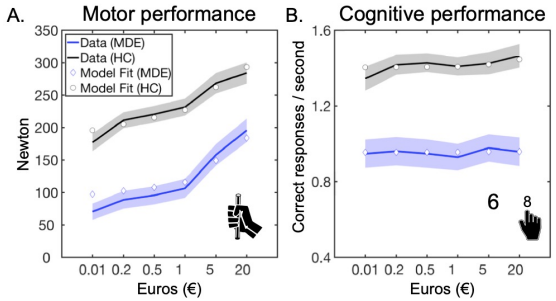
Comparison of populations

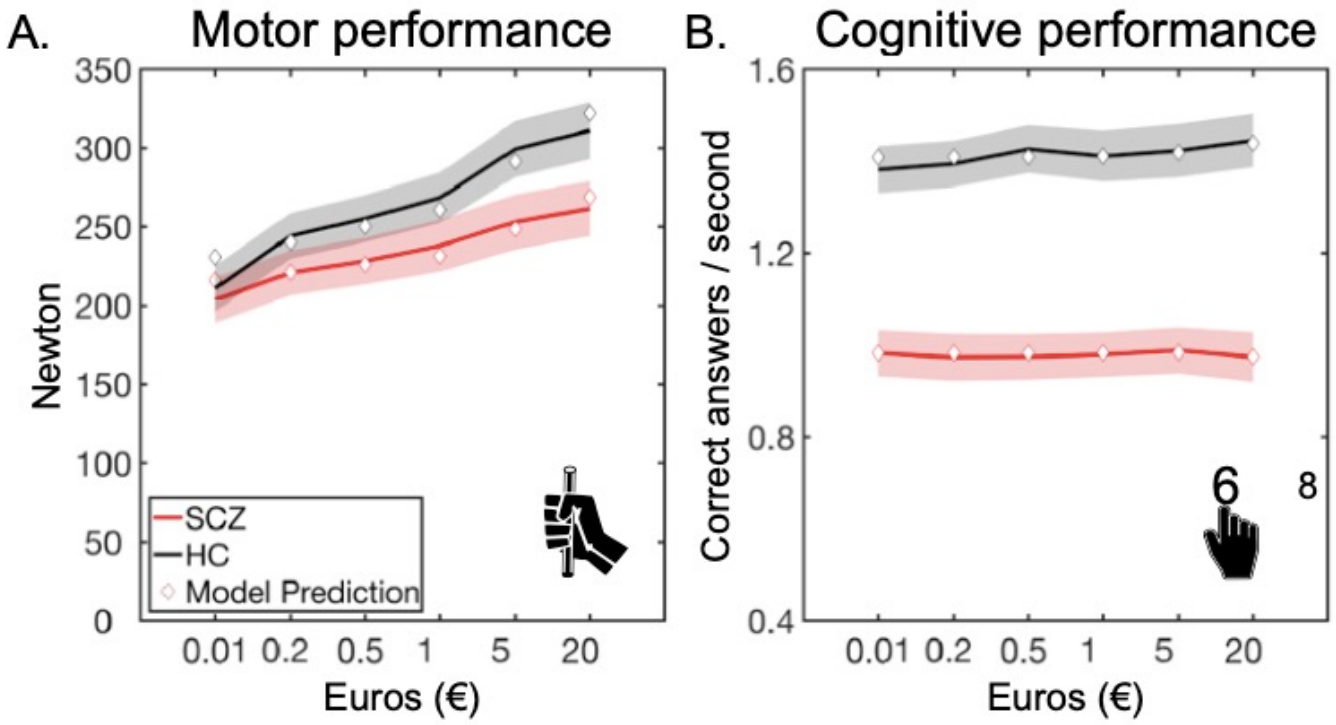


Interim conclusion

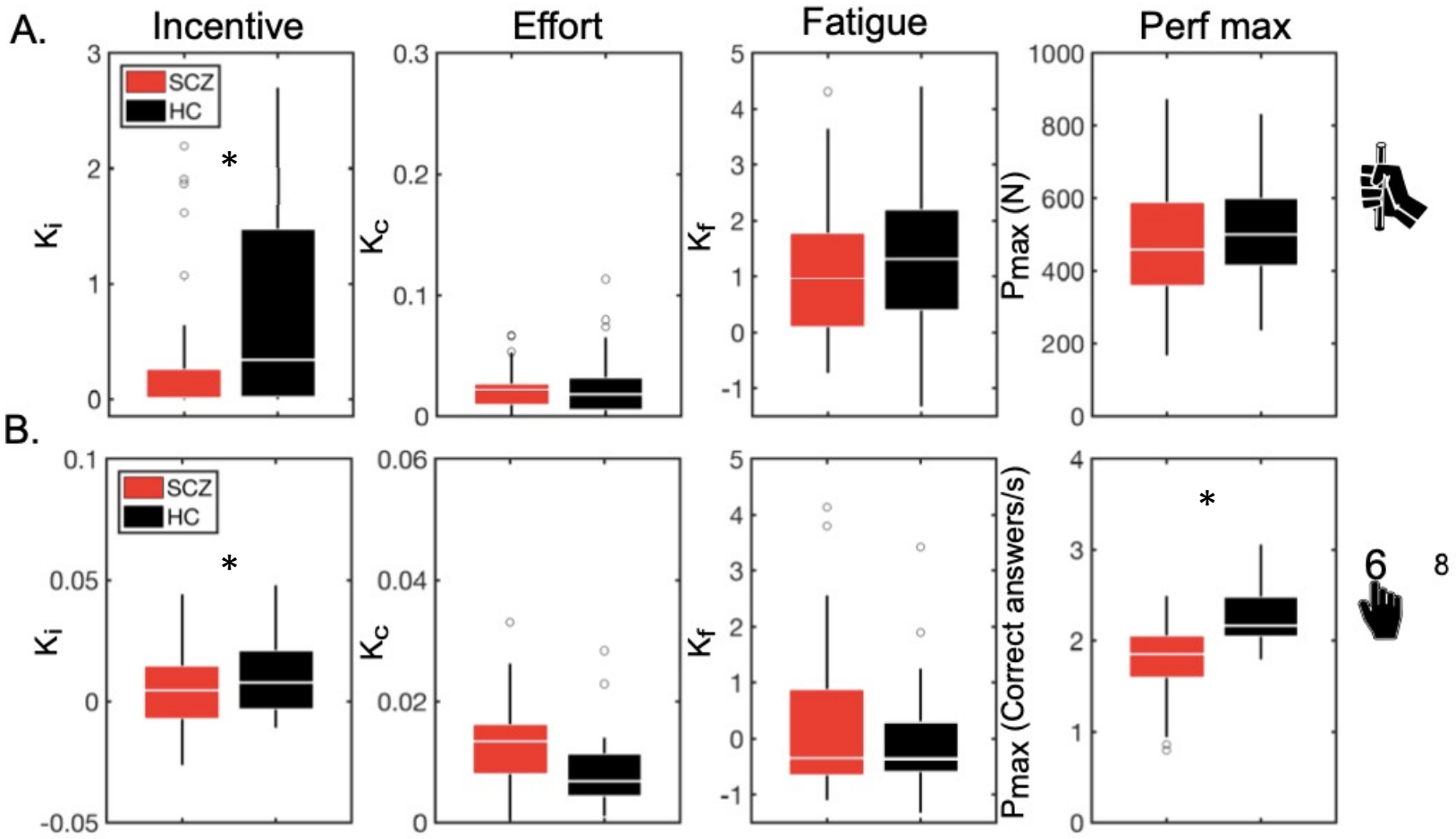
- Computational phenotyping of motivation
- Evaluating the same dimensions with (completely) different tasks
- Increased sensitivity to effort in depression in all tasks
- Ongoing project in depression :
    - Drug-naïve patients (N = 16 / 60)
    - Treatment-Resistant Depression (N = 34 / 90)
        - Different phenotype ?

Comparison of populations : patients with schizophrenia





Comparison of populations : patients with schizophrenia

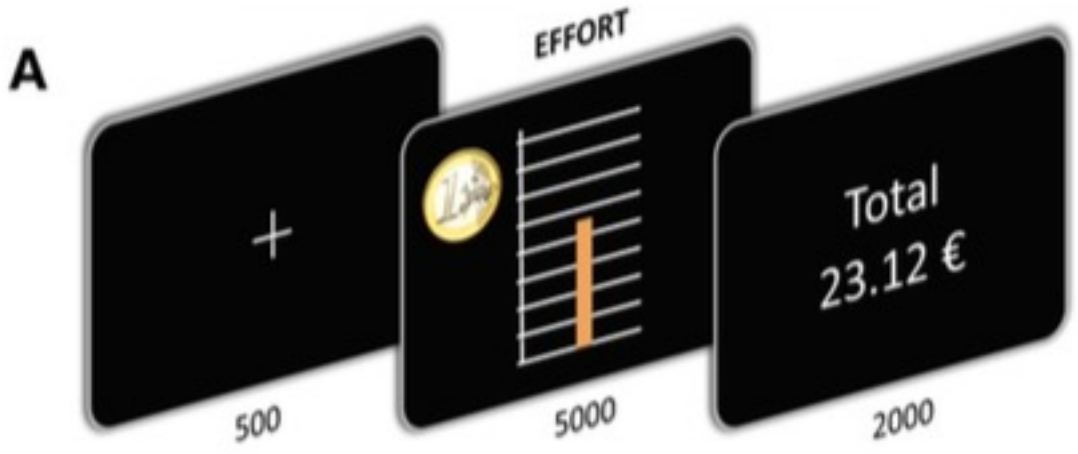


Characterization of treatments: in patients ?

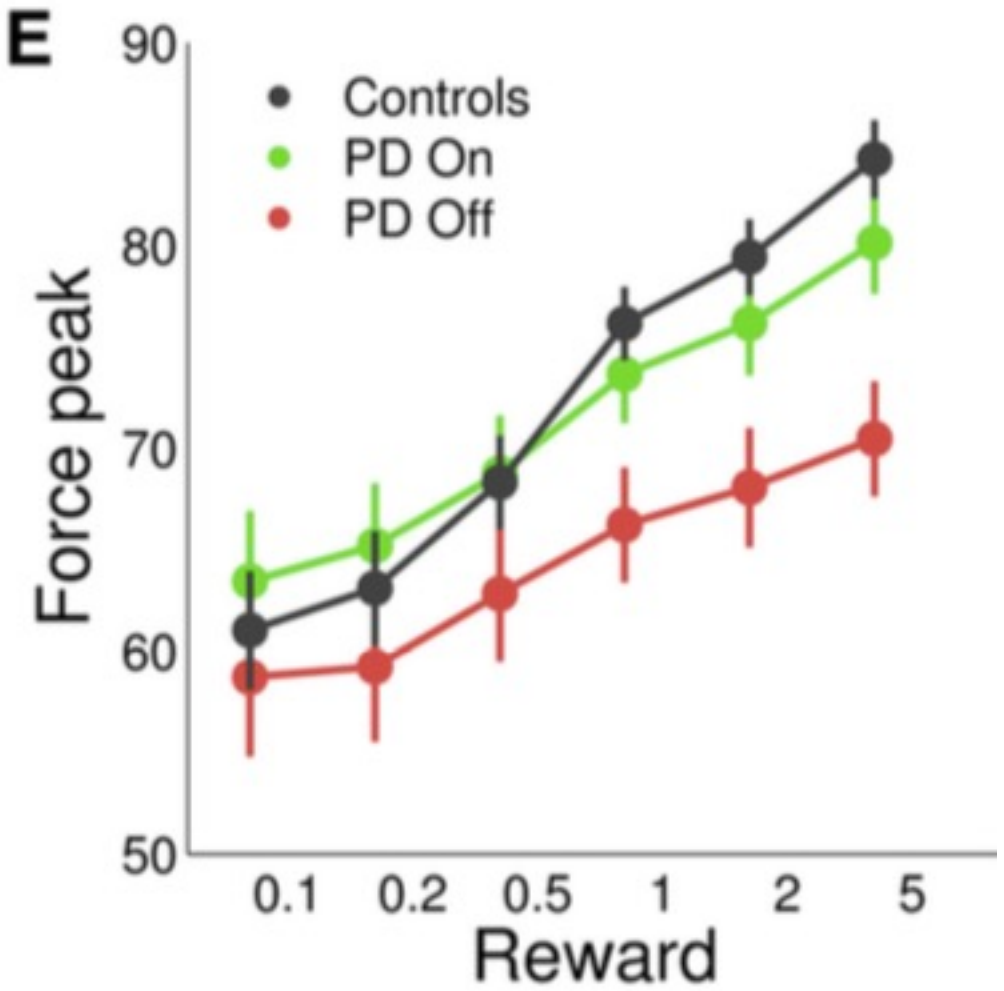
Behavioral/Cognitive

Computational Dissection of Dopamine Motor and Motivational Functions in Humans

Raphaël Le Bouc,[1,2,3] Lionel Rigoux,[1,2] Liane Schmidt,[5,6] Bertrand Degos,[2,4] Marie-Laure Welter,[2,4] Marie Vidailhet,[2,4] Jean Daunizeau,[1,2] and Mathias Pessiglione[1,2]



Effect of L-DOPA in Parkinson Disease



Le Bouc, Rigoux et al, 2016

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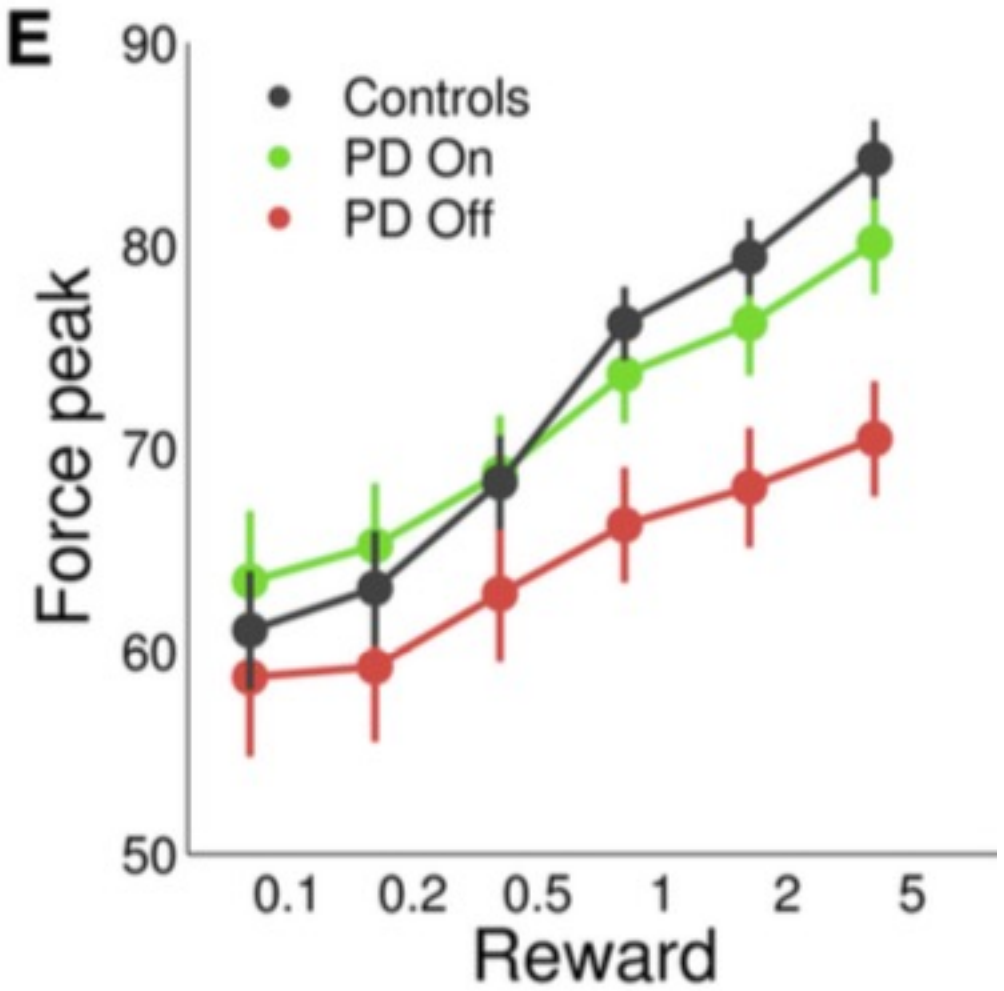

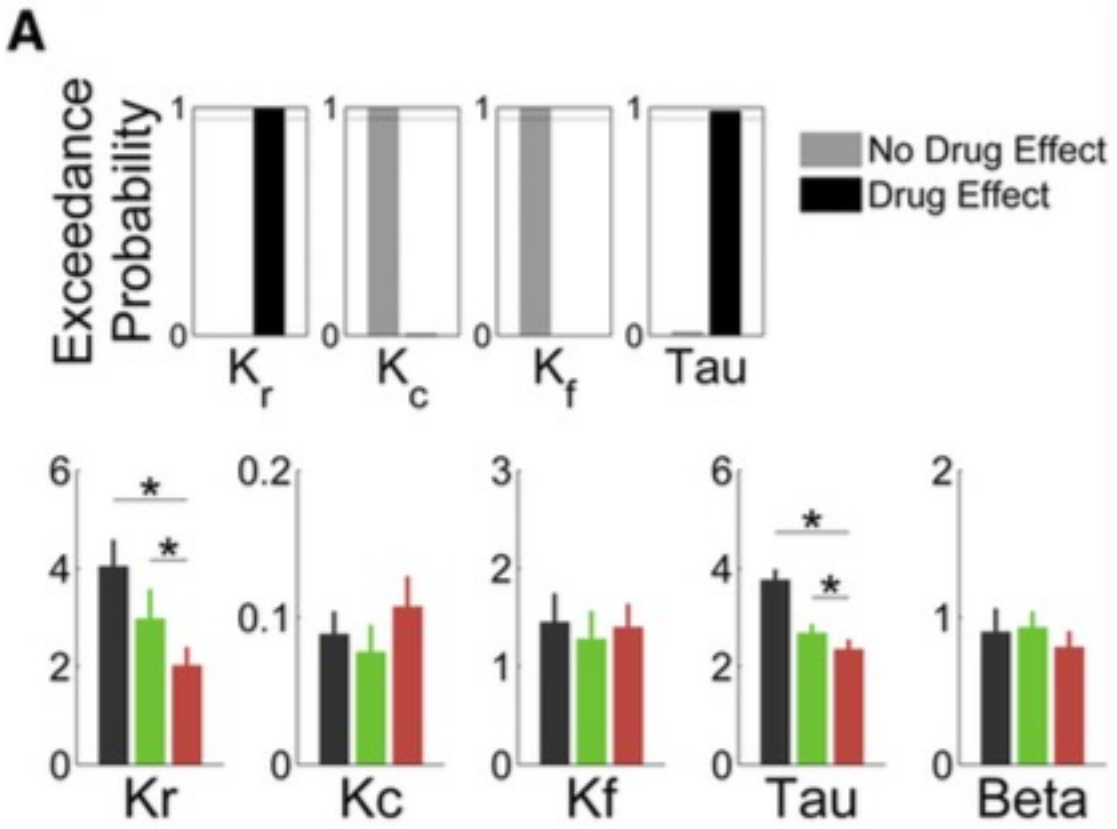

Le Bouc, Rigoux et al, 2016

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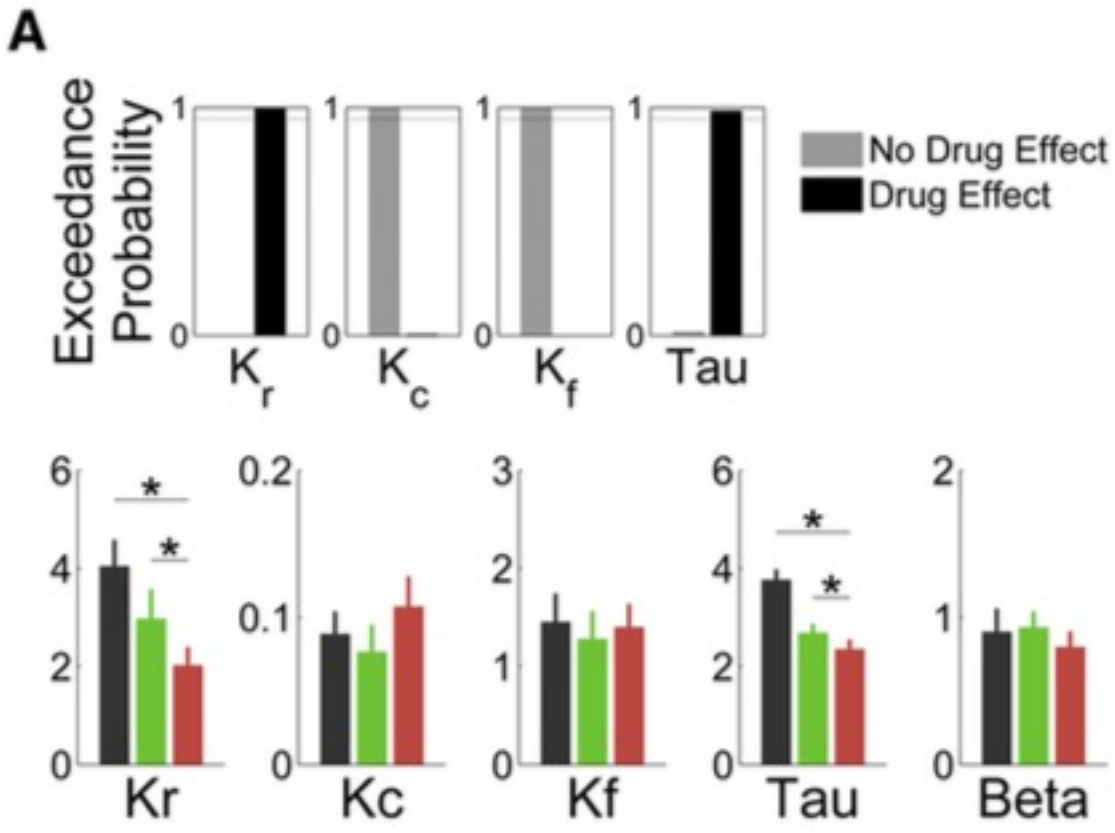
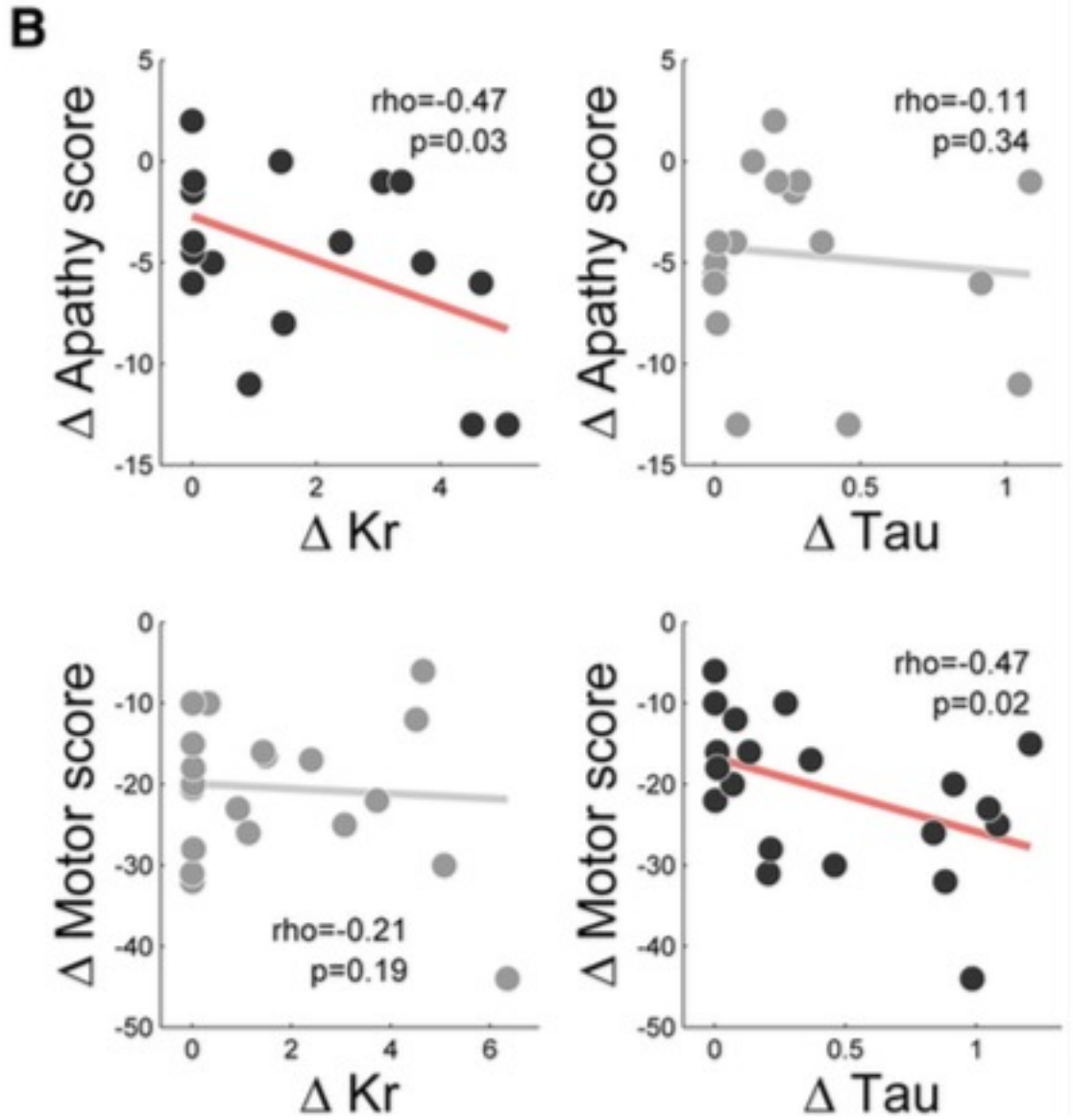




Le Bouc, Rigoux et al, 2016

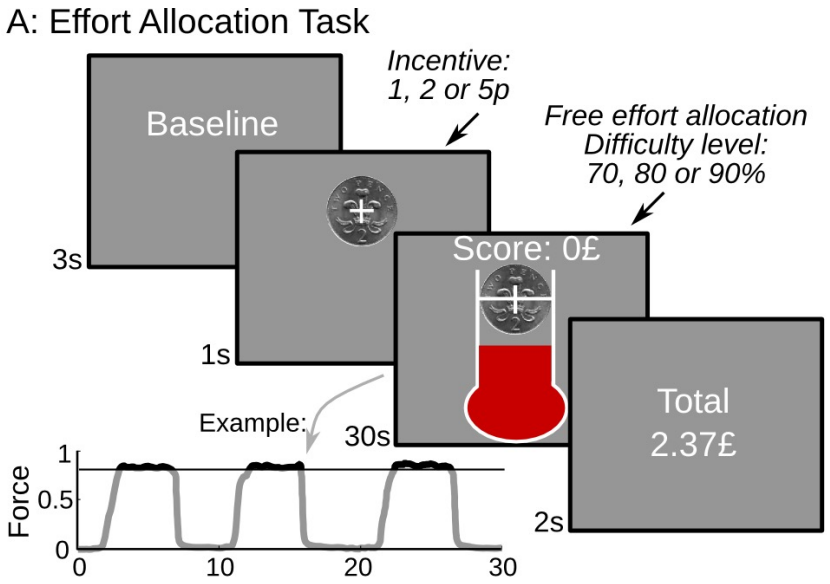
Characterization of treatments: in healthy volunteers ?

eLIFE elifesciences.org

RESEARCH ARTICLE

A specific role for serotonin in overcoming effort cost

Florent Meyniel[1,2,3*], Guy M Goodwin[4,5], JF William Deakin[6], Corinna Klinge[4,5], Christine MacFadyen[4,5], Holly Milligan[6], Emma Mullings[6], Mathias Pessiglione[1,2†], Raphaël Gaillard[7,8,9,10†]



- Citalopram vs placebo
- Up to 8 weeks !

Characterization of treatments: in healthy volunteers ?

eLIFE elifesciences.org RESEARCH ARTICLE

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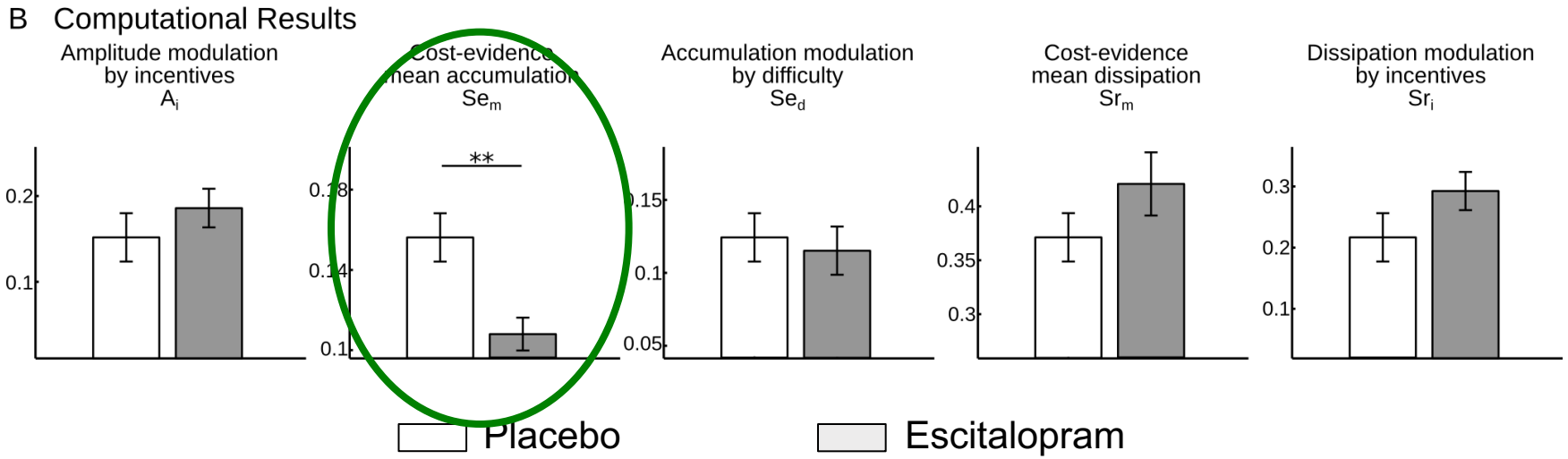
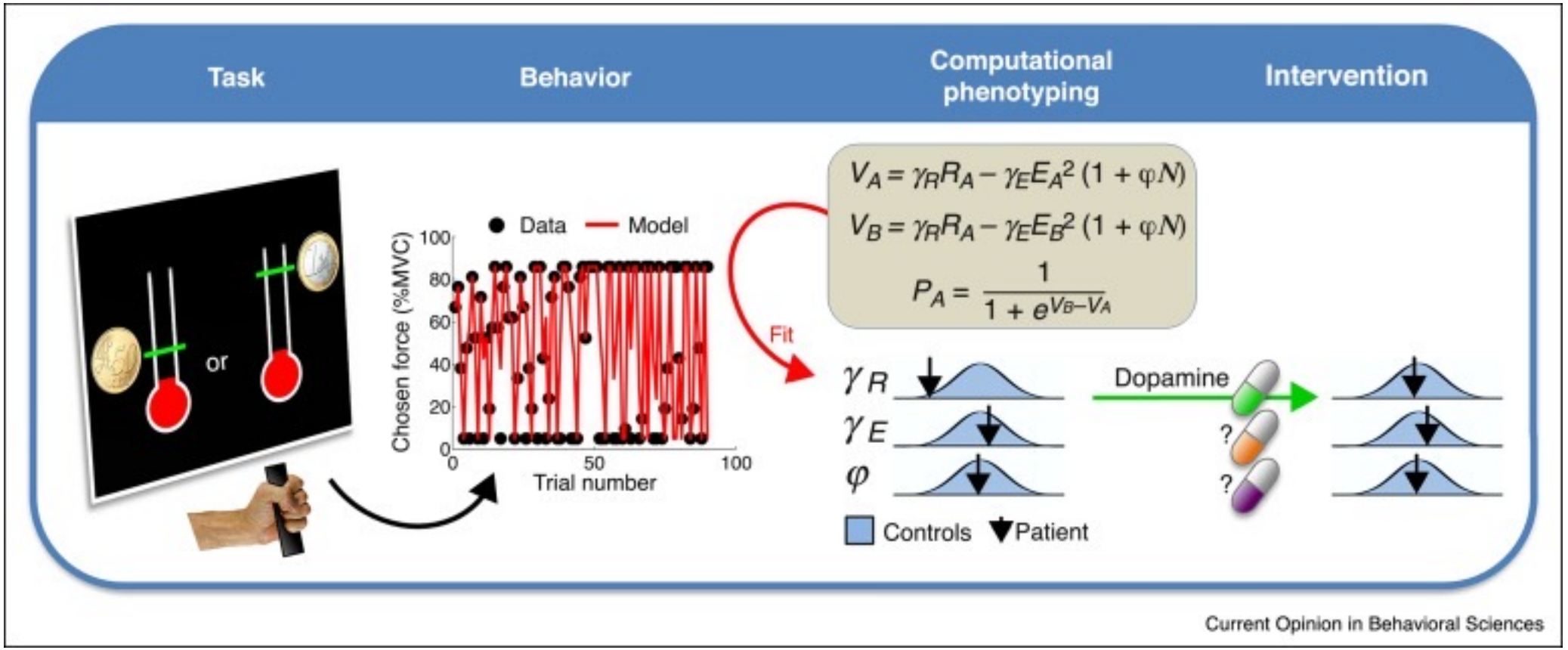
- Citalopram vs placebo
- Up to 8 weeks !



Useful from a clinical point of view?



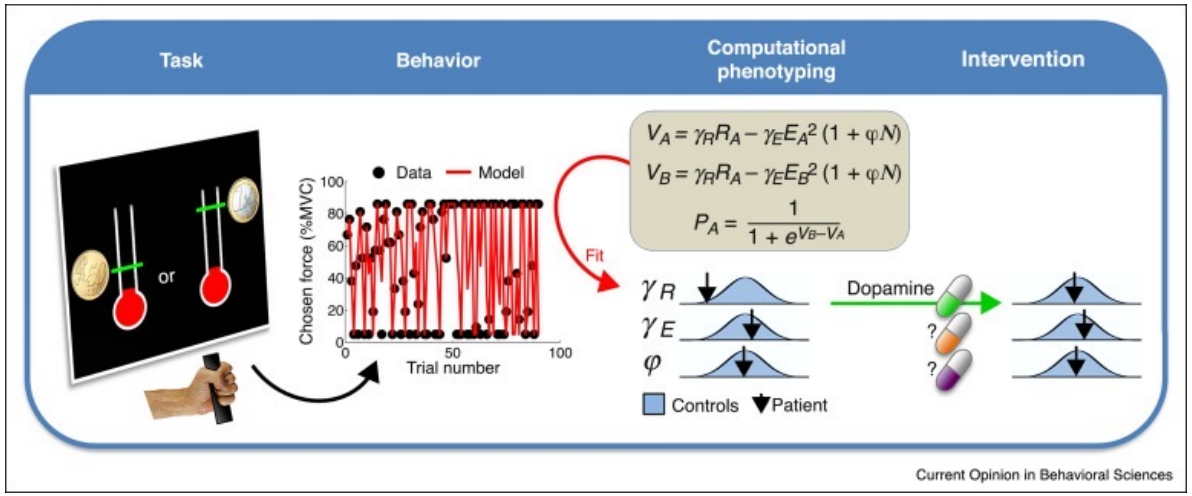
Pessiglione et al, 2018

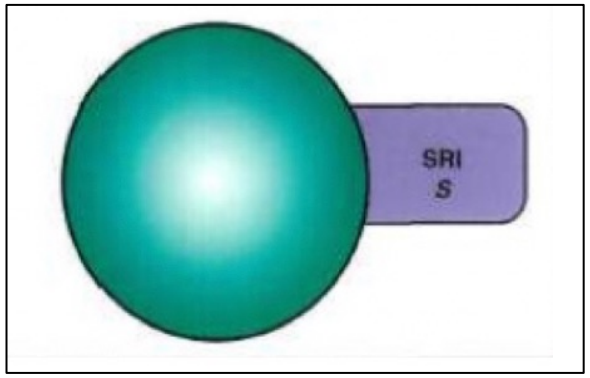
Stratidep Trial

(Investigator Initiated Trial grant)

Claire Jaffré

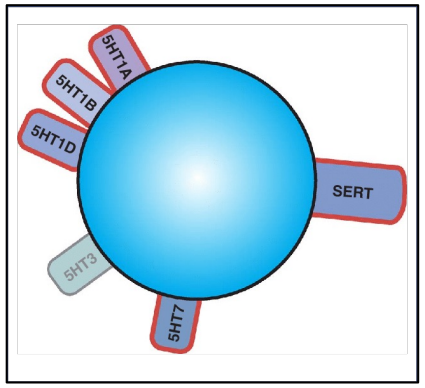
Useful from a clinical point of view: in depression ?





Escitalopram

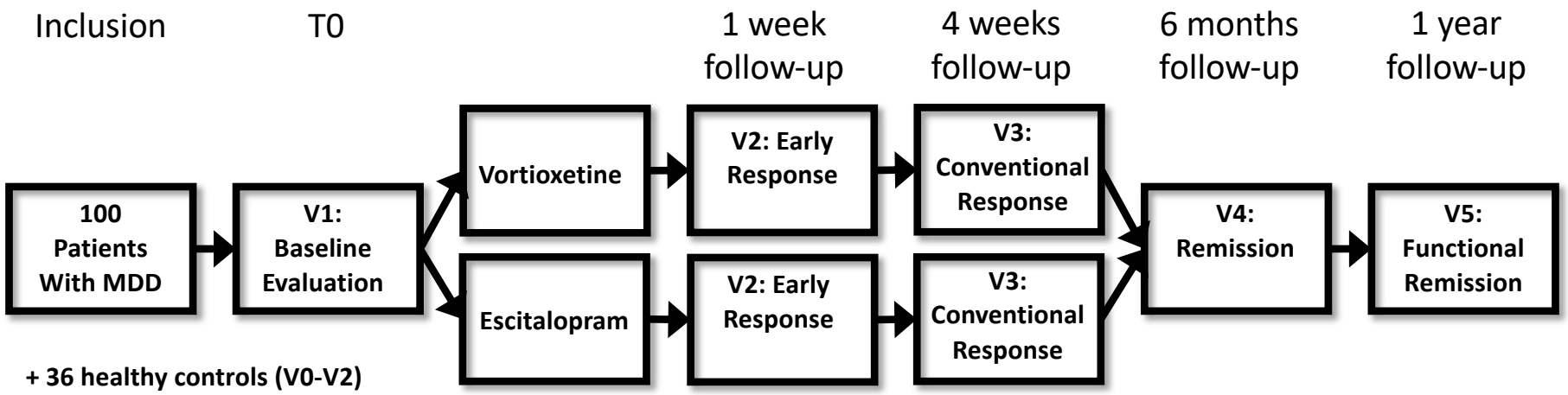
Vs.



Vortioxetine

?

Stratidep Trial



Clinical evaluation	✓	✓	Primary outcome ✓	✓	✓
MOTISCAN	✓	✓		✓	
Functional MRI	✓	✓			
Structural MRI	✓	✓		✓	

Stratidep Trial

- 3 types of objectives
  - Translational (bio-markers)
    - Predict clinical response based on initial phenotype / early changes
    - Predict functional remission
  - Basic science
    - Depression vs. controls… with fMRI
    - Escitalopram vs. vortioxetine
  - Ancillary
    - Bio-bank
    - Other neuro-imaging sequences

Stratidep Trial: timeline

- 3 types of objective
  - Translational (bio-markers)
    - Predict clinical response based on initial phenotype / early changes
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  - Basic science
    - Depression vs. controls… with fMRI
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    - Other neuro-imaging sequences

Thank you !

Why not try harder?

Computational approach to motivation deficits in neuro-psychiatric diseases.

Fabien VINCKIER

Université Paris Cité – GHU Paris Psychiatry & Neurosciences (Sainte-Anne Hospital)

Motivation Brain Behavior (Paris Brain Institute)