Tanulási paradigmák rágcsálókban kognitív zavarok modellezésére

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A magatartás modellezése, neurokémiája és gyógyszeres befolyásolása
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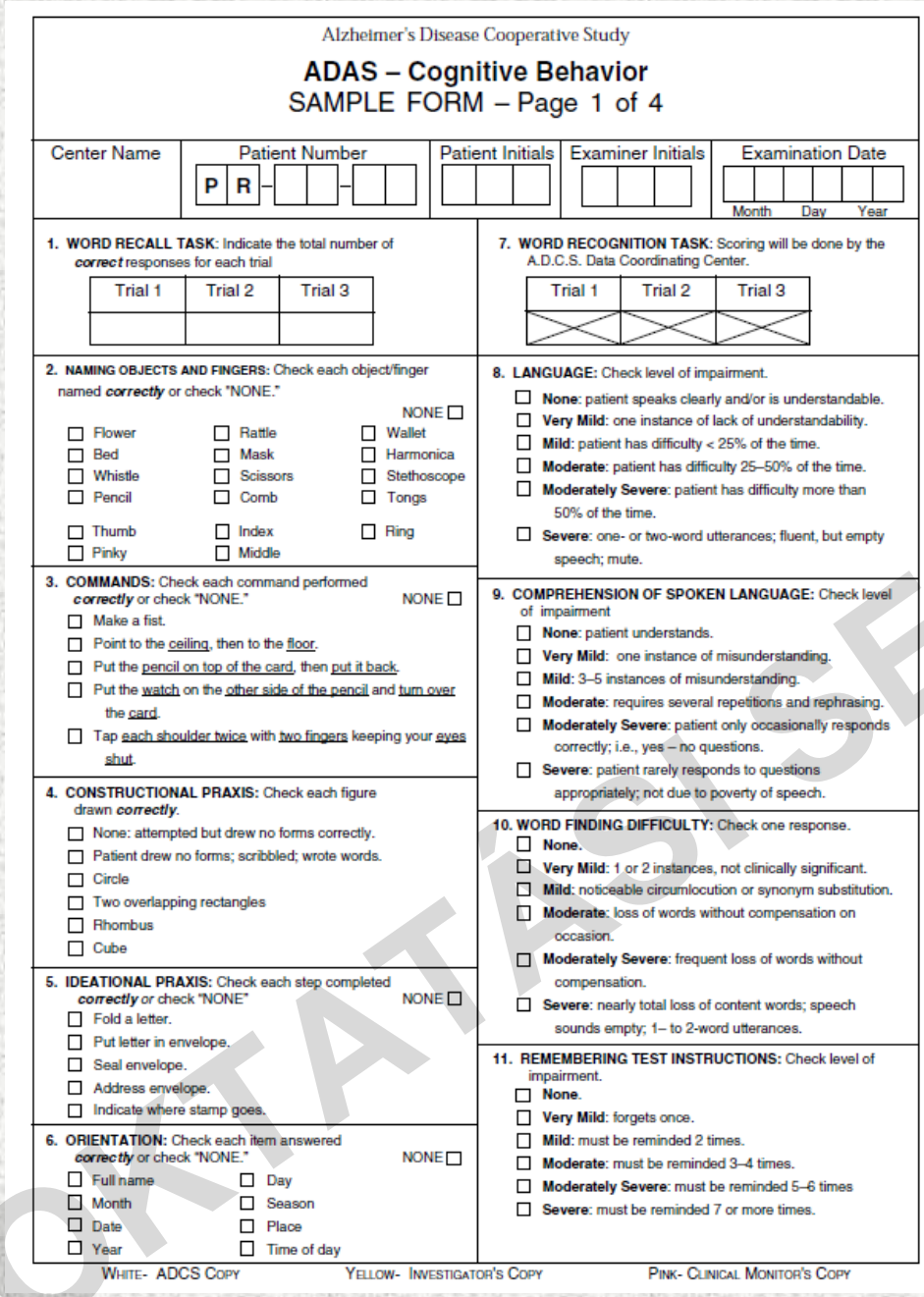
Kognitív zavarok kezelése

- mi a klinikai célpont?
  - a kognitív zavar nem betegség, hanem tünet
  - demencia (Alzheimer kór, AD)
- választás:
  - disease modifying (a patomechanizmust befolyásoljuk)
  - ➢ betegségmodell kell
    - ❖ pl. AD: transzgenikus állat, kolinerg lézió, β-amyloid adagolás
  - symptomatic (nem sérült, kompenzáló kognitív mechanizmusok aktiválása)
  - ➢ tünetmodell kell
- ha szimptomatikus javítás a cél, akkor a (közép)súlyos demencia kiesik
  - mild cognitive impairment (MCI) ill. korai AD
- bővíthető a target indikációk köre (betegségek melyekben a gondolkodás zavara áll fenn)
  - skizofrénia (CIAS)
  - ADHD
  - OCD
  - ASD
  - Parkinson kór
- eltérő a kognitív zavar mintázata
  pl. skizofrénia: MATRICS



Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior
SAMPLE FORM – Page 1 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

1. WORD RECALL TASK: Indicate the total number of ***correct*** responses for each trial

Trial 1	Trial 2	Trial 3

2. NAMING OBJECTS AND FINGERS: Check each object/finger named ***correctly*** or check "NONE."

NONE ☐

☐ Flower ☐ Rattle ☐ Wallet
☐ Bed ☐ Mask ☐ Harmonica
☐ Whistle ☐ Scissors ☐ Stethoscope
☐ Pencil ☐ Comb ☐ Tongs

☐ Thumb ☐ Index ☐ Ring
☐ Pinky ☐ Middle

3. COMMANDS: Check each command performed ***correctly*** or check "NONE." NONE ☐

☐ Make a fist.
☐ Point to the ceiling, then to the floor.
☐ Put the pencil on top of the card, then put it back.
☐ Put the watch on the other side of the pencil and turn over the card.
☐ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn ***correctly***.

☐ None: attempted but drew no forms correctly.
☐ Patient drew no forms; scribbled; wrote words.
☐ Circle
☐ Two overlapping rectangles
☐ Rhombus
☐ Cube

5. IDEATIONAL PRAXIS: Check each step completed ***correctly*** or check "NONE" NONE ☐

☐ Fold a letter.
☐ Put letter in envelope.
☐ Seal envelope.
☐ Address envelope.
☐ Indicate where stamp goes.

6. ORIENTATION: Check each item answered ***correctly*** or check "NONE." NONE ☐

☐ Full name ☐ Day
☐ Month ☐ Season
☐ Date ☐ Place
☐ Year ☐ Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

Trial 1	Trial 2	Trial 3
X	X	X

8. LANGUAGE: Check level of impairment.

☐ **None**: patient speaks clearly and/or is understandable.
☐ **Very Mild**: one instance of lack of understandability.
☐ **Mild**: patient has difficulty < 25% of the time.
☐ **Moderate**: patient has difficulty 25–50% of the time.
☐ **Moderately Severe**: patient has difficulty more than 50% of the time.
☐ **Severe**: one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

☐ **None**: patient understands.
☐ **Very Mild**: one instance of misunderstanding.
☐ **Mild**: 3–5 instances of misunderstanding.
☐ **Moderate**: requires several repetitions and rephrasing.
☐ **Moderately Severe**: patient only occasionally responds correctly; i.e., yes – no questions.
☐ **Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

☐ **None.**
☐ **Very Mild**: 1 or 2 instances, not clinically significant.
☐ **Mild**: noticeable circumlocution or synonym substitution.
☐ **Moderate**: loss of words without compensation on occasion.
☐ **Moderately Severe**: frequent loss of words without compensation.
☐ **Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

☐ **None.**
☐ **Very Mild**: forgets once.
☐ **Mild**: must be reminded 2 times.
☐ **Moderate**: must be reminded 3–4 times.
☐ **Moderately Severe**: must be reminded 5–6 times
☐ **Severe**: must be reminded 7 or more times.

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

ADAS-Cog

1. (verbal) working memory
2. semantic memory
3. procedural/executive function
4. visuospatial/executive
5. executive (planning)
6. episodic memory
7. working memory/attention
8. language
9. language
10. language
11. language

Millan et al., 2012, Nature Reviews | Drug Discovery

Table 1 | **Main characteristics of cognitive impairment in psychiatric disorders, and a comparison with PD and AD***

	Attention and/or vigilance	Working memory	Executive function	Episodic memory	Semantic memory	Visual memory	Verbal memory	Fear extinction	Processing speed	Procedural memory	Social cognition (theory of mind)	Language	References
Major depression	+(+)	++	++	++	+	+	+(+)	0/+?	++(+)	+	+(+)	+	17,5
Bipolar disorder	++(+)	++	++	++	+	+	++	+?	++	0	++	++	19 ←
Schizophrenia	+++ M	+++M	+++M	+++	++	+(+)M	+++M	++	++M	+	+++M	+++	29,5 ←
ASD	+++	+	+++	++	+	+	+(+)	+(+)	+ ++	0/+	+++	+++	23,5 ←
ADHD	+++	++	+++	0/+	+	++	++	+	++	+	+	0/+	19 ←
OCD	+++(↑)	+(+)	++	+	0/+	+	0/+	++	++	++	+	0/+	17
PTSD	+++(↑)	+(+)	+(+)	++	+	+	++(+)	+++	+	0	0/+	0	17
Panic disorder	+++(↑)	+	0/+	+	0/+	0/+	+	++	++	0	0	0	11,5
GAD	+	+	0	0	+	+	+	+	0	0	0/+	0	6,5
Parkinson's disease	++	++(+)	++	+	0/+	+	+	0?	+++	+++	+(+)	+(+)	19 ←
Alzheimer's disease	+(+)	+(+)	+(+)	+++	+++	+++	++(+)	0?	+	+	+	++	21 ←
	26,5 (17,5)	19	20,5	17,5	12,5	14	18,5	14	20,5	9	15	13,5	

Modellezési kihívások - 1

- eltérő terminológia:
  - klinika:
    explicit (deklaratív) – implicit (procedurális) memória
    epizodikus – szemantikus
    dysexecutive syndrome
  - állat:
    appetitive – aversive learning
    spatial – non spatial learning
    associative learning (contextual, cue-related)
    recognition task

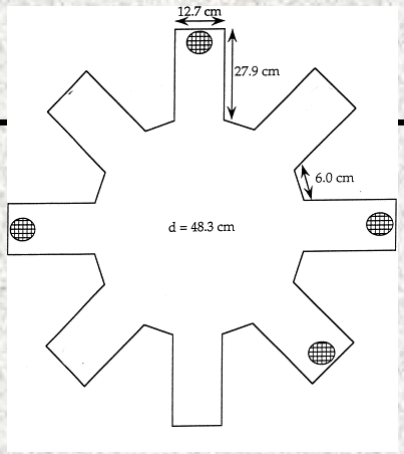
    working – reference memory
    short term – long term memory

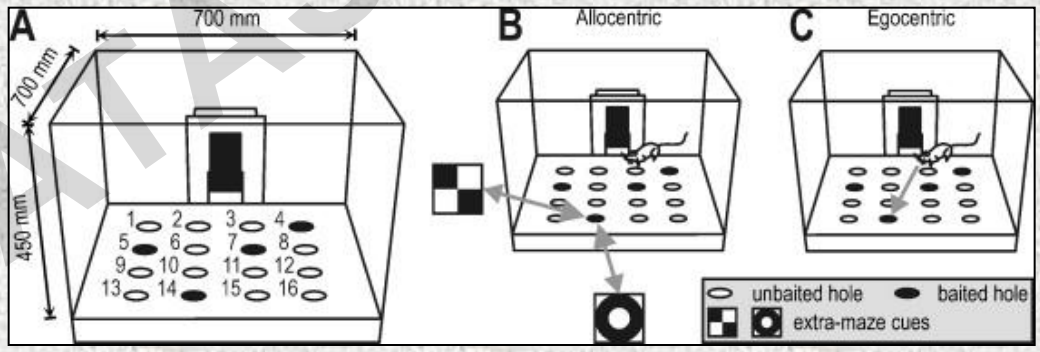
Kognitív funkciók rágcsálómodelljei

working memory	Y-maze spontán alternáció
spatial learning & memory	Morris water-maze water-labirynth
visual learning & memory	object recognition *place recognition*
attention & information processing	5-CSRTT PPI
fear extinction (aversive learning)	fear conditioning
social memory	social recognition
executive (problem solving &reasoning)	attentional set shifting
executive (decision making)	rat gambling
impulsivity (response inhibition)	delayed discounting
procedural	rotarod learning

Kognitív funkciók rágcsálómodelljei

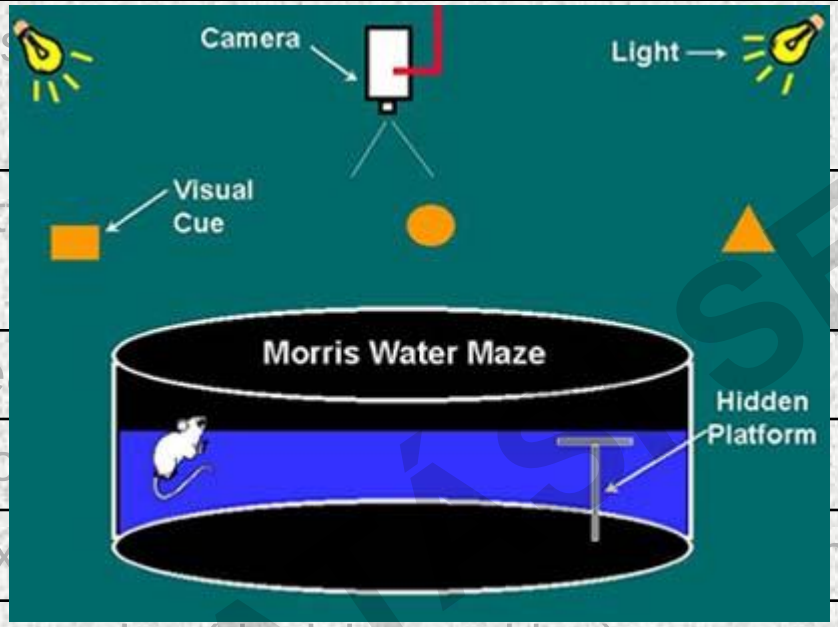
working memory	Y-maze spontán alternáció radial arm maze hole-board





Kognitív funkciók rágcsálómodelljei

working memory	Y-maze spontán alternáció
spatial learning & memory	Morris water-maze water-labirynth
vis	
at	
fe	
sc	
ex ng)	
executive (decision making)	
impulsivity (response inhibition)	delayed discounting
procedural	rotarod learning

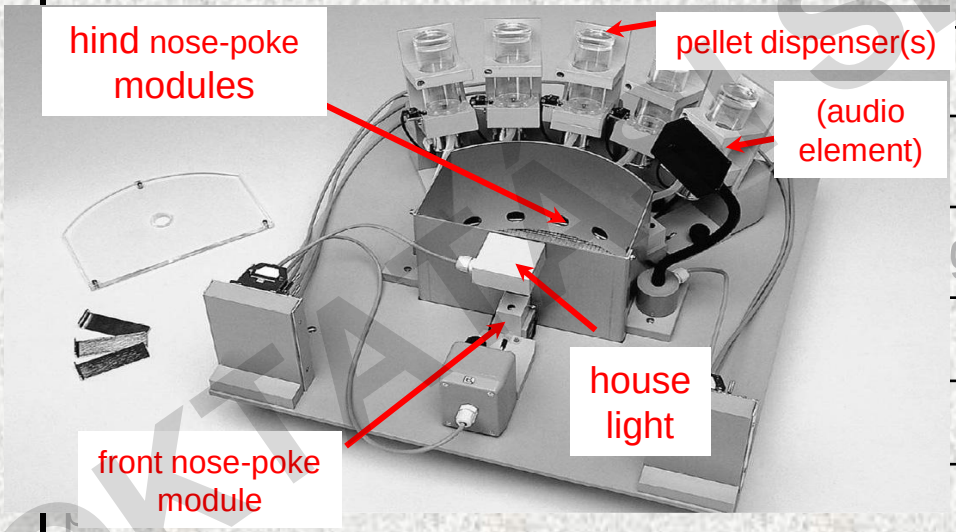


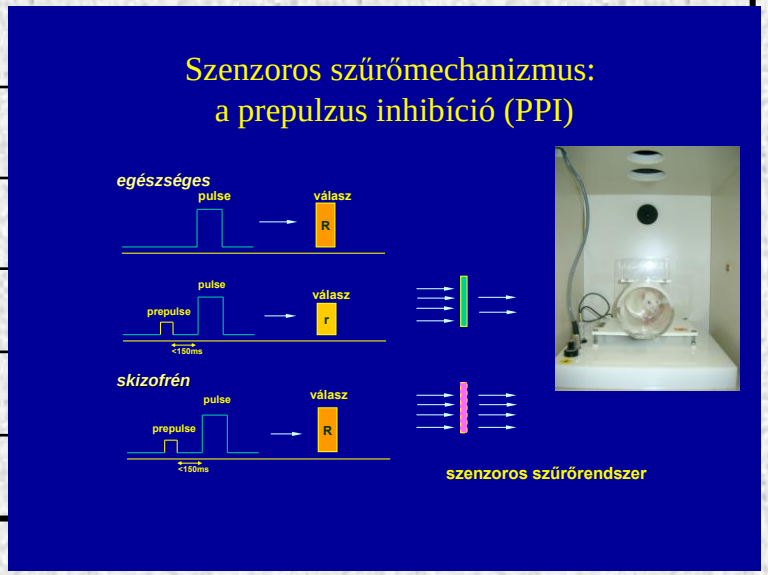
Kognitív funkciók rágcsálómodelljei

working memory	Y-maze spontán alternáció
spatial learning & memory	Morris water-maze water-labirynth
visual learning & memory	novel object recognition place recognition
atten sing	
fear e ng)	
socia	
executive (problem solving &reasoning)	
executive (decision making)	
impulsivity (response inhibition)	
procedural	rotarod learning

Kognitív funkciók rágcsálómodelljei

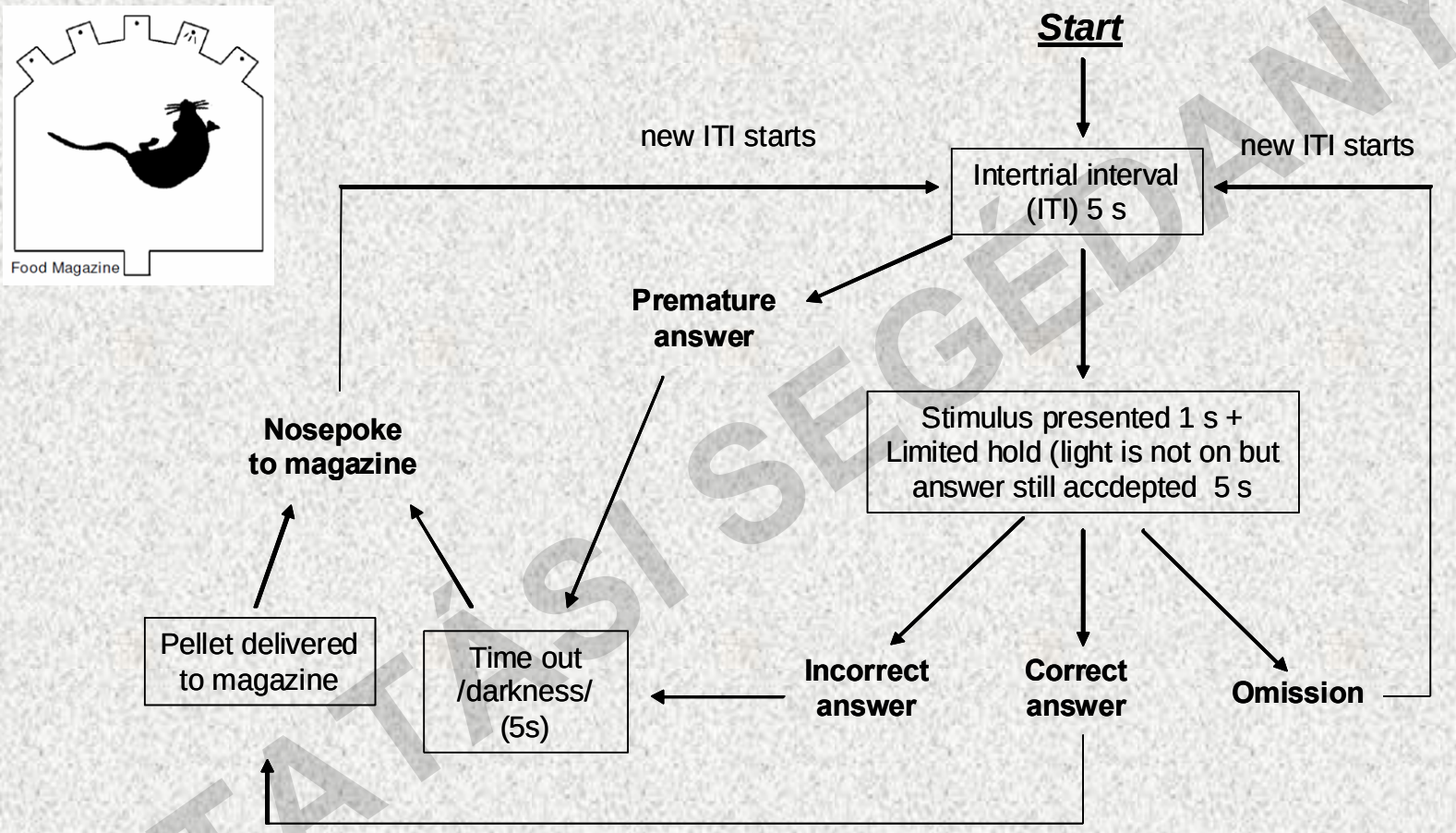
working memory	Y-maze spontán alternáció
spatial learning & memory	Morris water-maze water-labirynth
visual learning & memory	object recognition *place recognition*
attention & information processing	5-CSRTT PPI





Decreased stimulus duration (SD) paradigm

SD ↓ from 1 to 0.5 s ⇒ ***attention load*** ↑ ⇒ correct% ↓ (c.a. 10%)

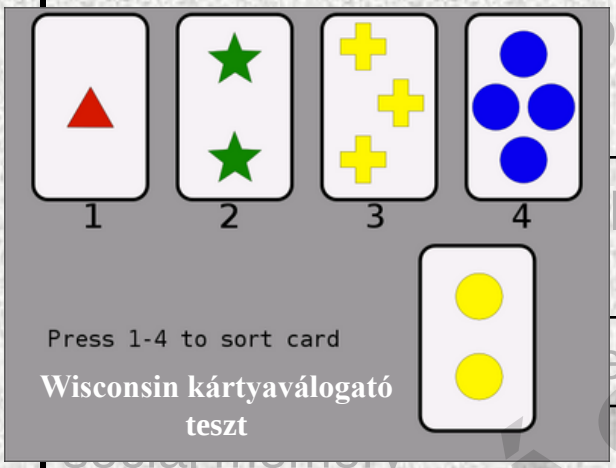


Increased ITI paradigm (ITI paradigm)

ITI ↑ from 5 to 10 s ⇒ ***impulsivity load*** ↑ ⇒ premature% ↑ (c.a. 45%)

Kognitív f csálómodelljei

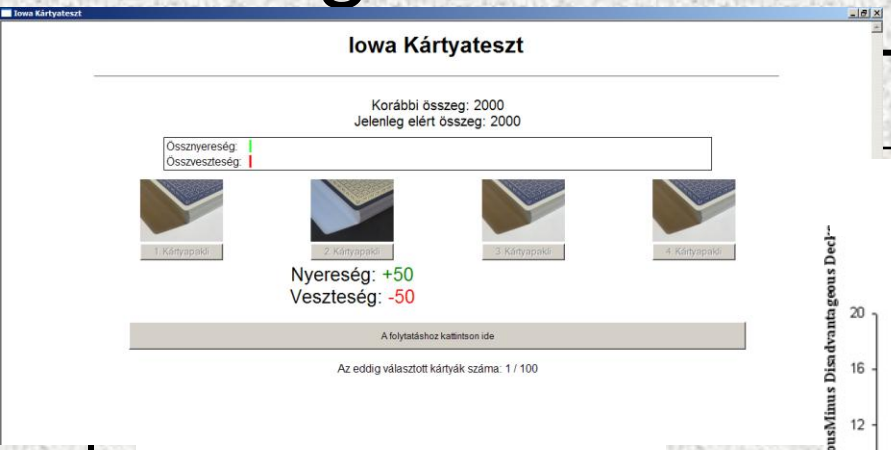
working memory	-maze spontán alternáció
spatial learning & me	orris water-maze
	ater-labirynth
	ry
	proc
	e lea
executive (problem solving &reasoning)	attentional set shifting
executive (decision making)	rat gambling
impulsivity (response inhibition)	delayed discounting
procedural	rotarod learning



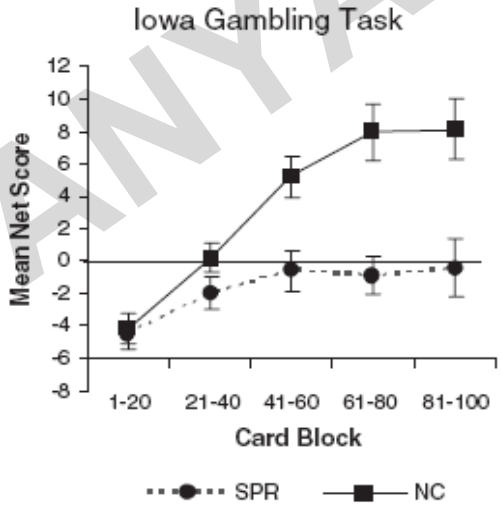
Wisconsin kártyaválogató teszt

Feladat	Dimenzió			
	releváns (szabály)		irreleváns	
	+	-		
egyszerű diszkrimináció	forgács	homok		
összetett diszkrimináció	forgács	homok	**citrom**	**fahéj**
megfordítás	homok	forgács	**citrom**	**fahéj**
intradimenzionális váltás	polisztirol	gyöngyök	**menta**	**paprika**
megfordítás	gyöngyök	hungarocell	**menta**	**paprika**
extradimenzionális váltás	gyömbér	vanilia	**tealevél**	**papírcafatok**
megfordítás	vanilia	gyömbér	**tealevél**	**papírcafatok**

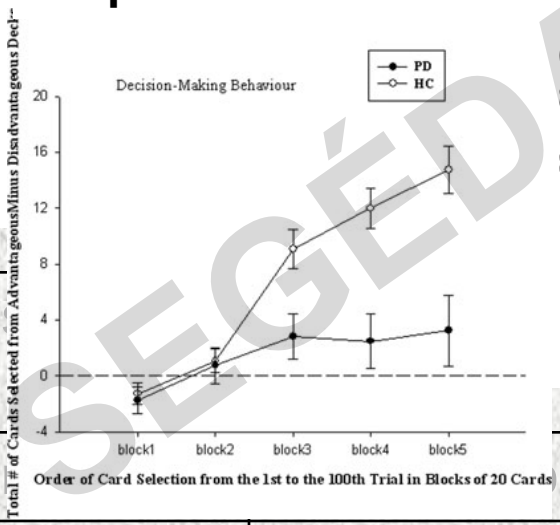
Kognitív funkciók rágcsálómodelljei



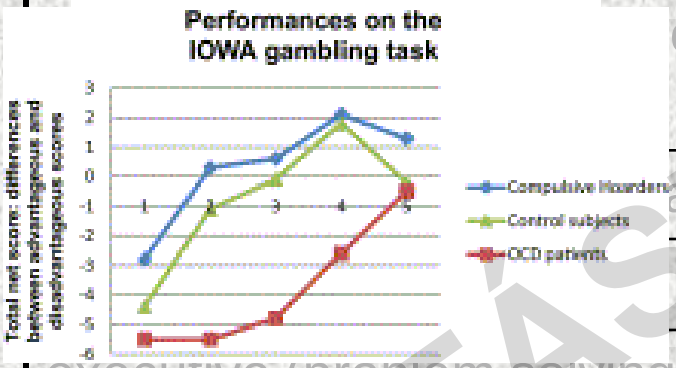
skizofrének



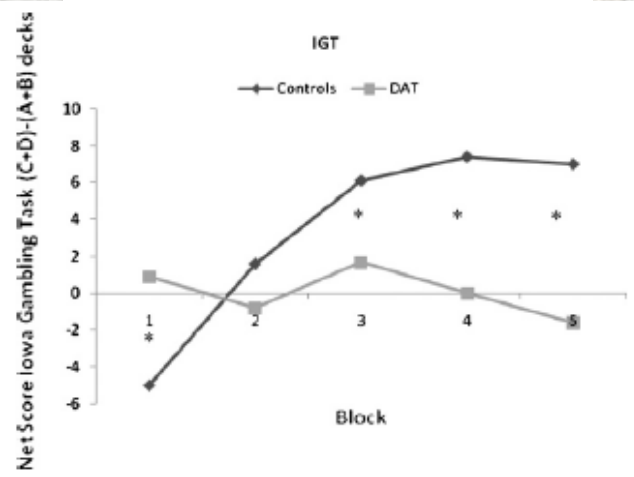
parkinsonosok



OCD betegek

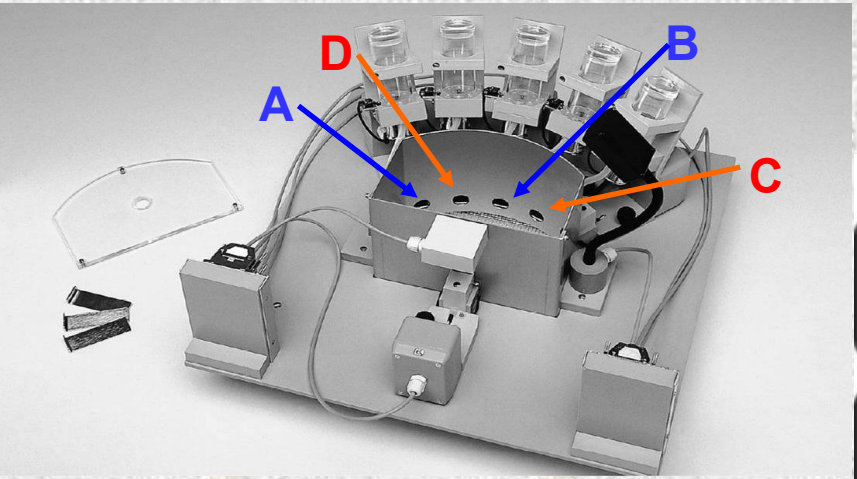


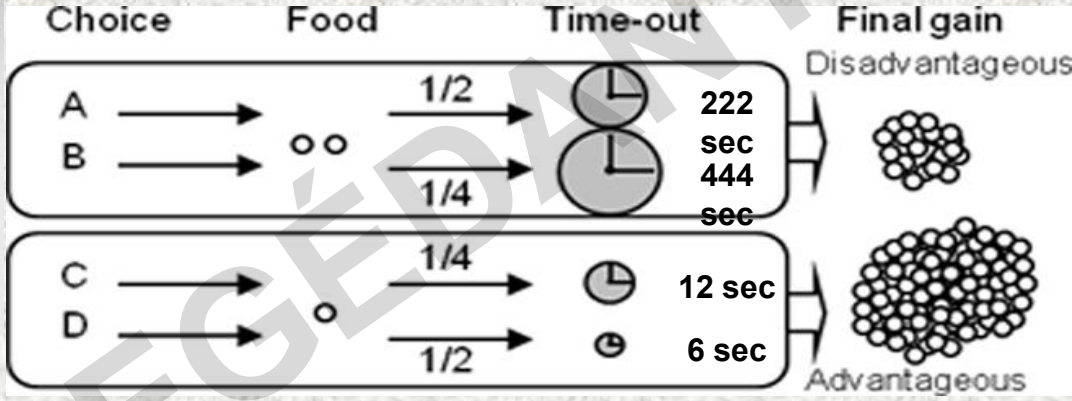
korai alzheimeresek

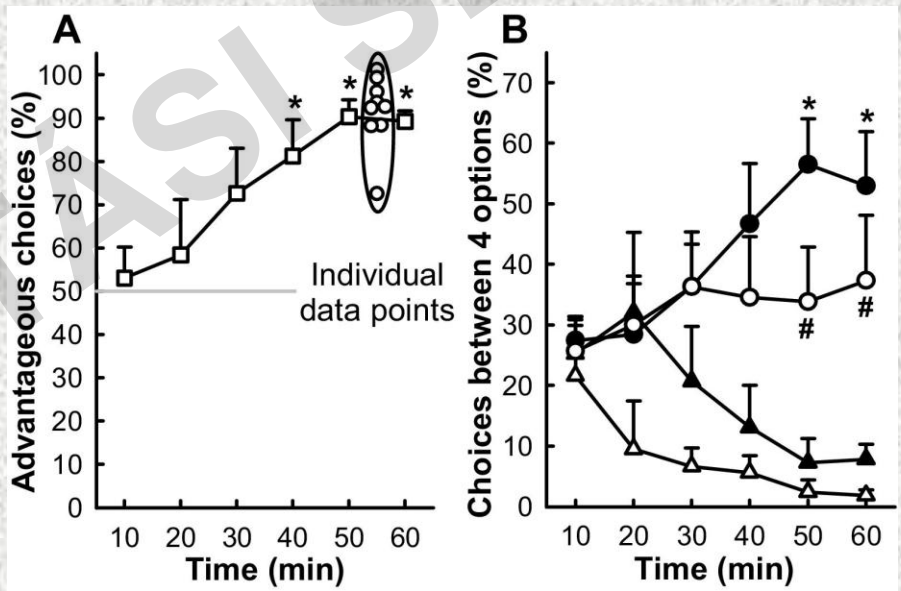


executive (problem solving &reasoning)	attentio
executive (decision making)	rat gam
impulsivity (response inhibition)	delayed
procedural	rotarod

Rat Gambling Test

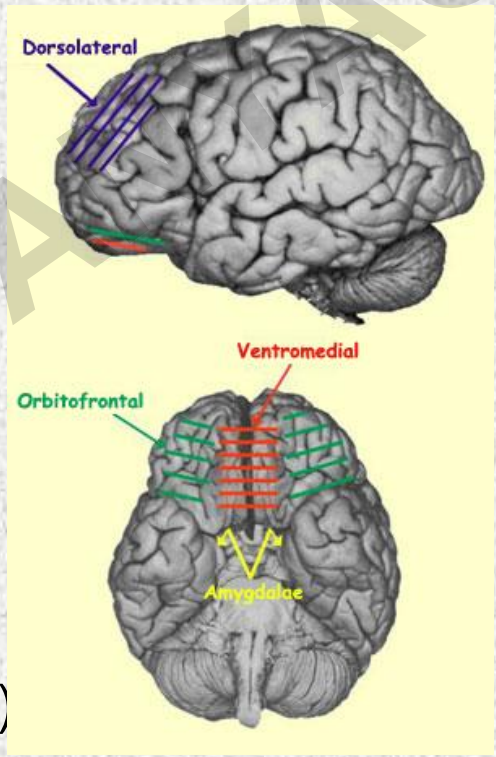






WCST és IGT

- végrehajtó funkciókat mérnek (de nem ugyanazt)
- prefrontális kéreghez kötődő funkciók
- csökkent teljesítmény („dysexecutive syndrome”):
  - skizofrénia
  - ADHD
  - OCD
  - ASD (Aspergen is!)
  - mild cognitive impairment/korai demencia
  - Parkinson kór
- jellemzően endofenotípus
- premorbid állapotban már detektálható (biomarker)
- nem érintett rokonokban is megjelenik a deficit
- a „legjobban árazható” deficit



Modellezési kihívások - 2

- a rágcsáló modellek validitása
  - predictive validity
  - face validity
  - construct validity

- mivel rontunk?
  - farmakológiai ágens
  - léziók
  - gén expresszió módosítás
  - idős kor
  - feladat nehezítése
  - populáció felosztása

- mivel validáljuk a modellt?
  - AchE gátlók (donepezil)?
  - memantin?
  - nootrópikumok (piracetám)?

- több modell kell

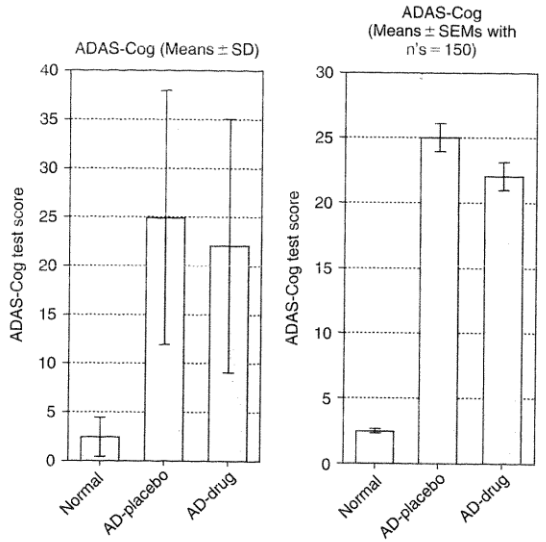


Figure 4.3 Examination of the variability associated with changes in ADAS-Cog scores of normal aged-matched controls, and AD patients treated with donepezil or placebo. Means and standard deviations of ADAS-Cog scores in non-demented controls and AD patients treated with donepezil or placebo were estimated from several studies.[238–244]

Gyógyszerkutatási kihívások

Mi legyen a target??

- több évtizedes kutatási terület csekély eredménnyel
  - AchE gátlók
  - memantin
  - nootrópikumok
- irodalom bőséges választékot kínál
  ...már 30 éve
- multi-target megközelítés hozhat javulást
  - kombinációk
  - többes hatású anyagok

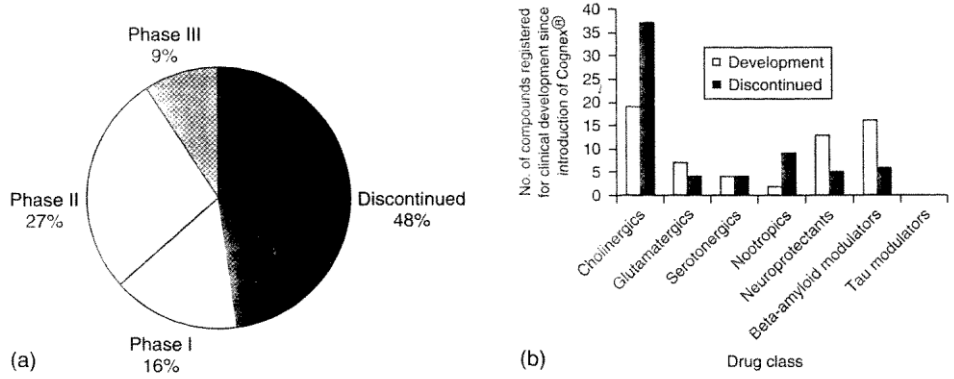


Figure 4.1 Compounds that reached clinical development as potential pharmacotherapies for cognitive impairments in AD since the introduction of Cognex®, divided according to (a) stage of development, and (b) by drug class.

Gyógyszerkutatási kihívások

kognítív javító szer keresése (betegségre) illetve kognitív rontó ágens keresése (biztonságfarmakológia, neurotoxicitás) eltérő modelleket igényel

javítás

- eltérő kognitív funkciók defektesek
- ezeket a kognitív funkciókat kell modellezni
- gyakran bonyolult paradigmák

rontás

- nem kívánt mellékhatásra szűrünk
- érzékeny, de egyszerű modell kell
- általánosan is jellemezheti a kognitív működést

spontán alternáció

új tárgyfelismerés, helyfelismerés

passzív elkerülés