

Psychopharmacology:
Drugs That Impact
Cognition

Neuropsychiatry: A
Comprehensive Update

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Outline by Diler Acar, MD



Brigham and Women's Hospital
Founding Member, Mass General Brigham



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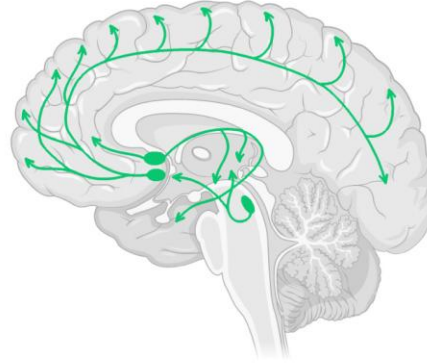


Mass General Brigham

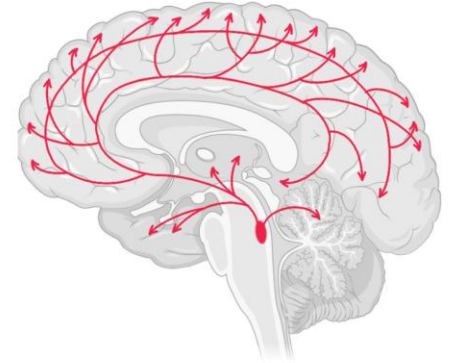
- I have no financial relationships with a commercial interest to disclose
- Investigational uses for FDA-approved medications are discussed

Introduction to Cognitive Psychopharmacology

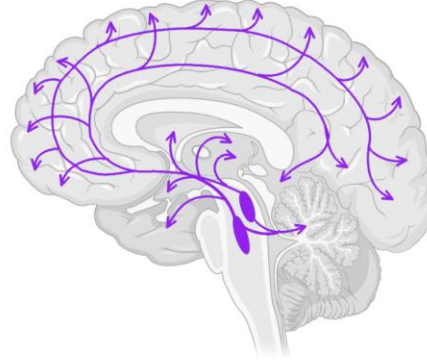
(a) cholinergic



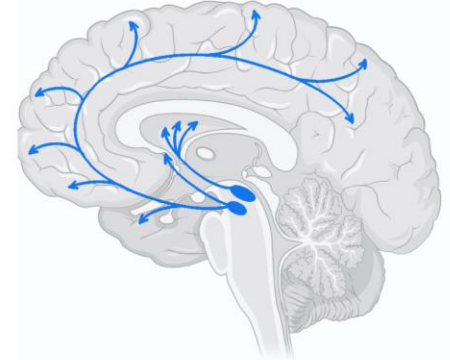
(b) noradrenergic



(c) serotonergic



(d) dopaminergic



Neural networks modulated by fast-signaling neurotransmitters

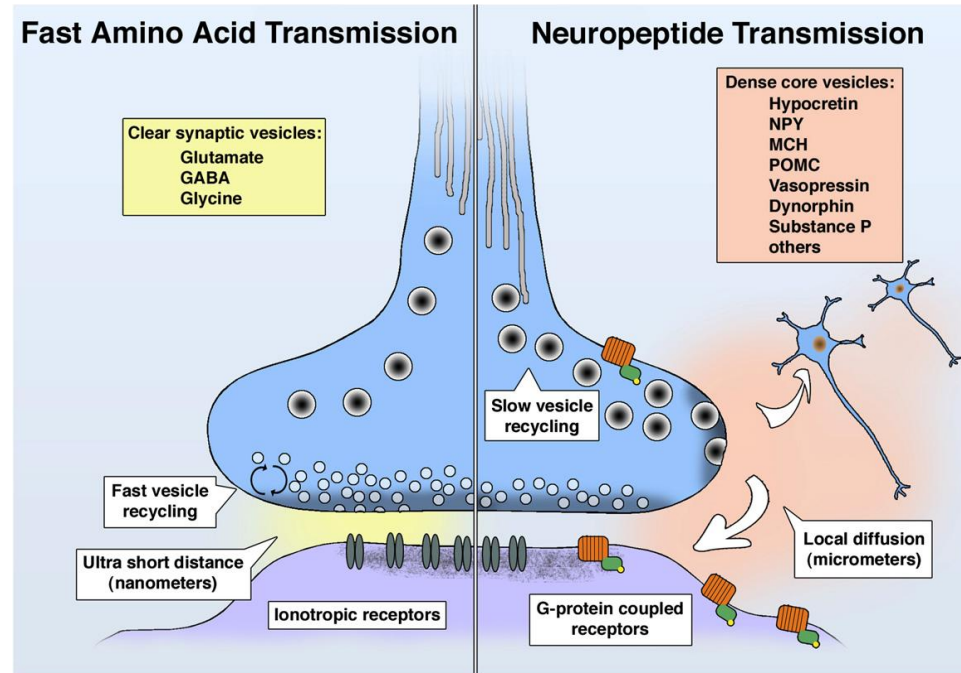
- Connectivity of neuronal networks in cerebral cortex, hippocampus and striatum is mediated by fast signaling transmission
- Glutamate (excitatory) ionotropic receptors: NMDA, AMPA, Kainate
- Gamma aminobutyric acid (inhibitory; GABA): GABA-a, GABA-b

Neuronal networks modulated by slow-modulatory neurotransmitters

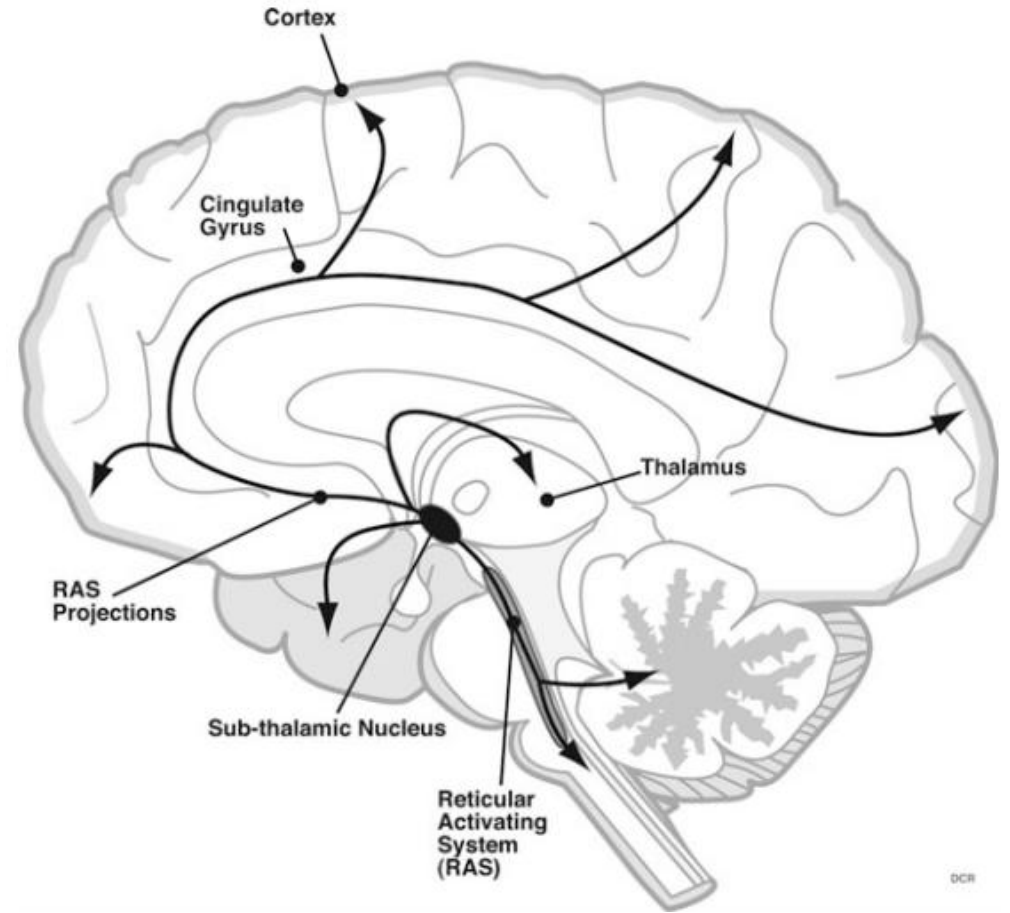
- Acetylcholine: nicotinic, muscarinic
- Dopamine: D1-D5
- Noradrenaline: alpha 1, 2; beta 1, 2
- Serotonin (5-hydroxytryptamine; 5-HT): 5-HT1a, 5-HT1b, 5-HT2a, etc.

Neuropeptides

- Very slow modulators/co-transmitters
- Cholecystokinin(CCK) co-transmitter for DA: CCK-A, CCK-B
- Neuropeptide Y co-transmitter for NA: NPY1R, NPY2R
- Vasoactive intestinal polypeptide (VIP) co-transmitter for Ach: VPAC1, VPAC2
- Oxytocin, Vasopressin: OXTR, V1-V3



Disorders of Wakefulness



Neurotransmitters

1. Cholinergic Stimulation

Mesopontine projections/ARAS → thalamus

2. Catecholamine augmentation (e.g., dopamine, norepinephrine, epinephrine)

Ventral tegmental nucleus → limbic structures, striatum, frontal cortex

3. Glutamate system modulation

Antagonism/agonism of NMDA-, GABA- receptors -> widespread through neocortex

Cognitive enhancers

1. Cholinergic Stimulation

Alterations in cholinergic transmission implicated in delirium, fluctuations in DLB, cognitive deficits in severe TBI

Rx: Acetylcholinesterase inhibitors, choline, nicotine/derivatives

2. Catecholamine augmentation (e.g., dopamine, norepinephrine, epinephrine)

Low levels of DA/NE implicated in decreased arousal, sleep latency, REM sleep

Rx: Amantadine, bromocriptine, apomorphine, desipramine

3. Glutamate system modulation

Positive modulation of GABA has paradoxical effect for some DOC

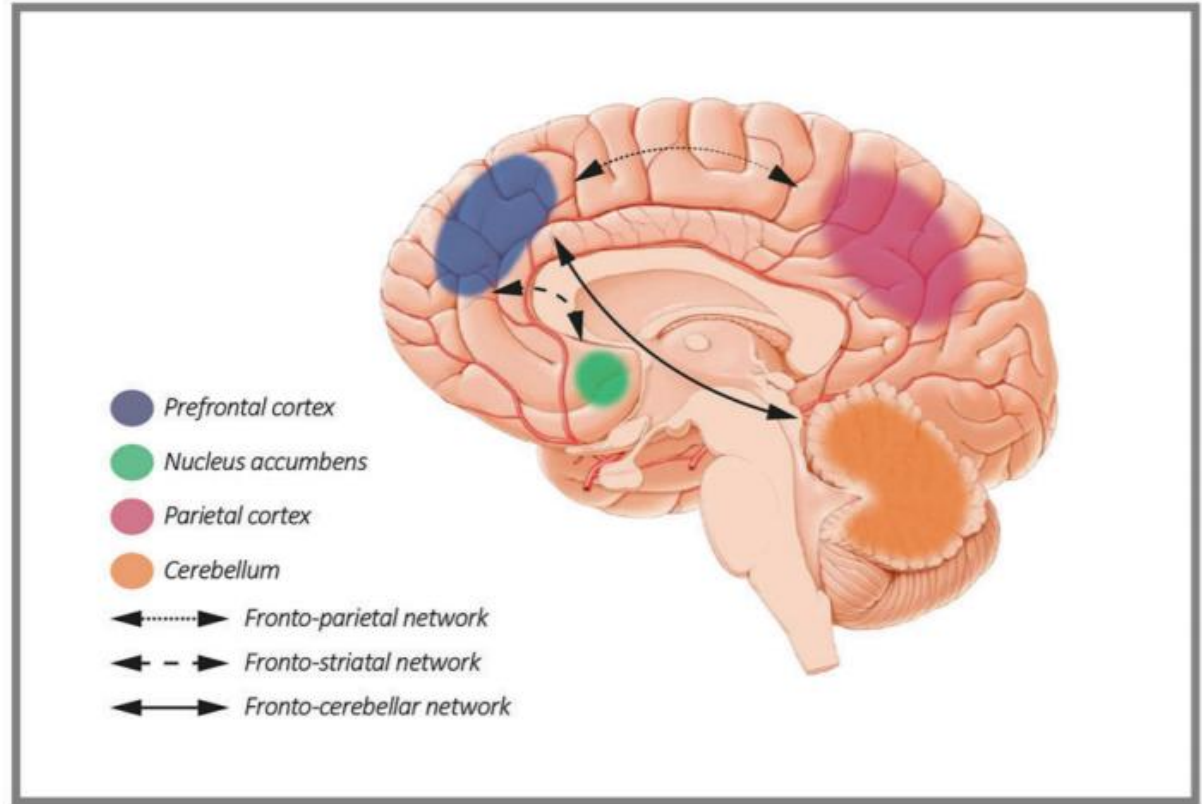
Rx: Zolpidem, baclofen, memantine, riluzole

Psychopharmacology

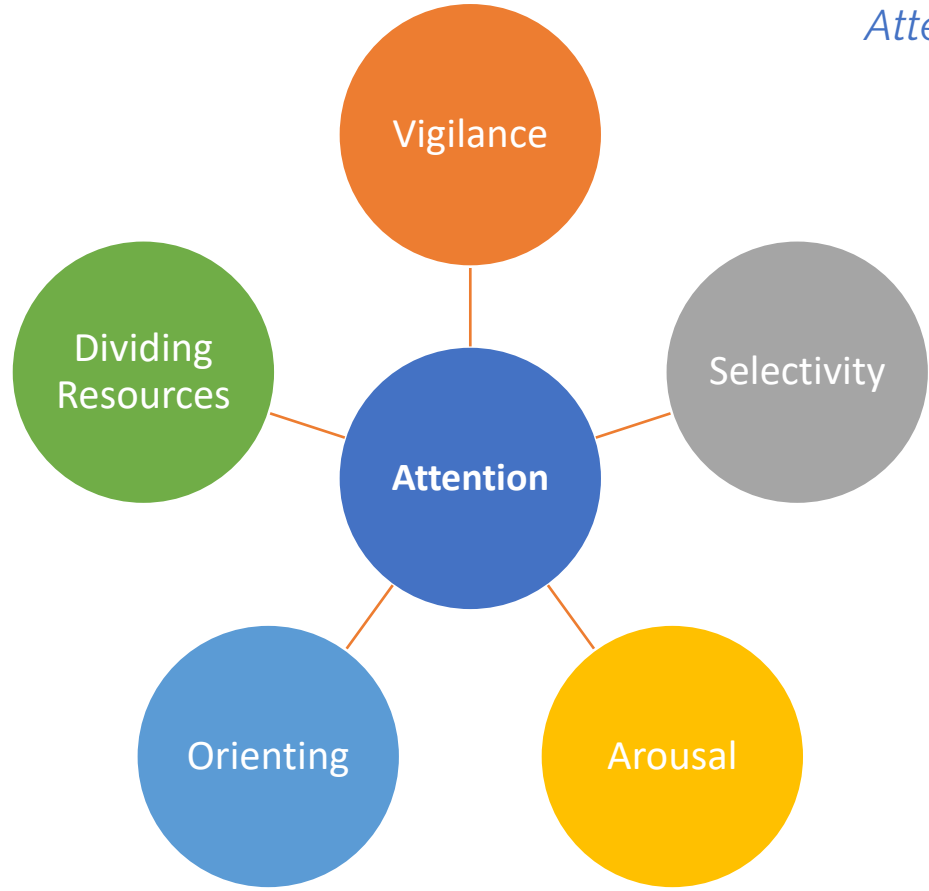
▶ Modafinil/Armodafanil

- Inhibition of DA and NE transporters
- *FDA indications:* Excessive daytime sleepiness related to narcolepsy, shift work sleep disorder, adjunct treatment for OSA
- *Off-label considerations:*
 - Cognition in Chronic Fatigue Syndrome, MS, other autoimmune/inflammatory conditions
 - Fatigue in MS, PD

Disorders of Attention



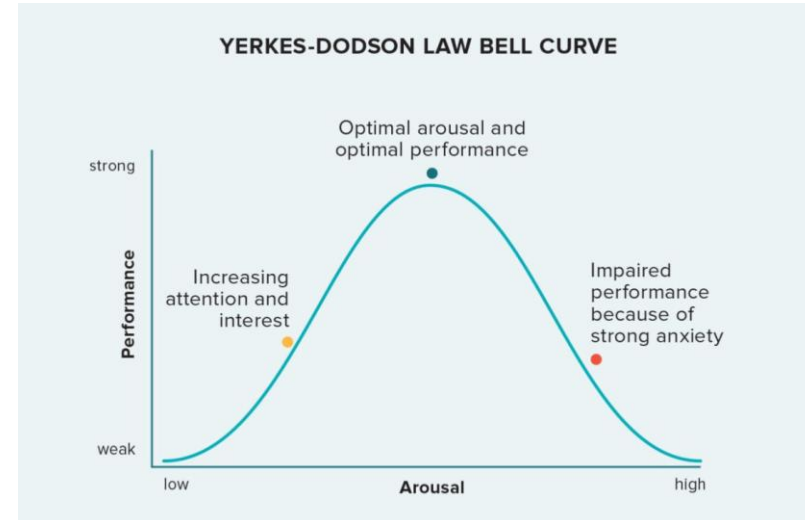
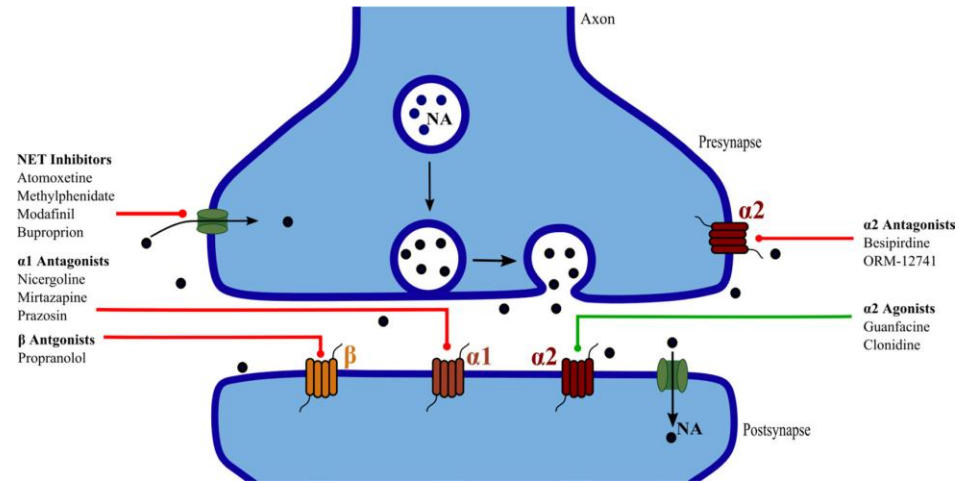
Background



Psychopharmacology

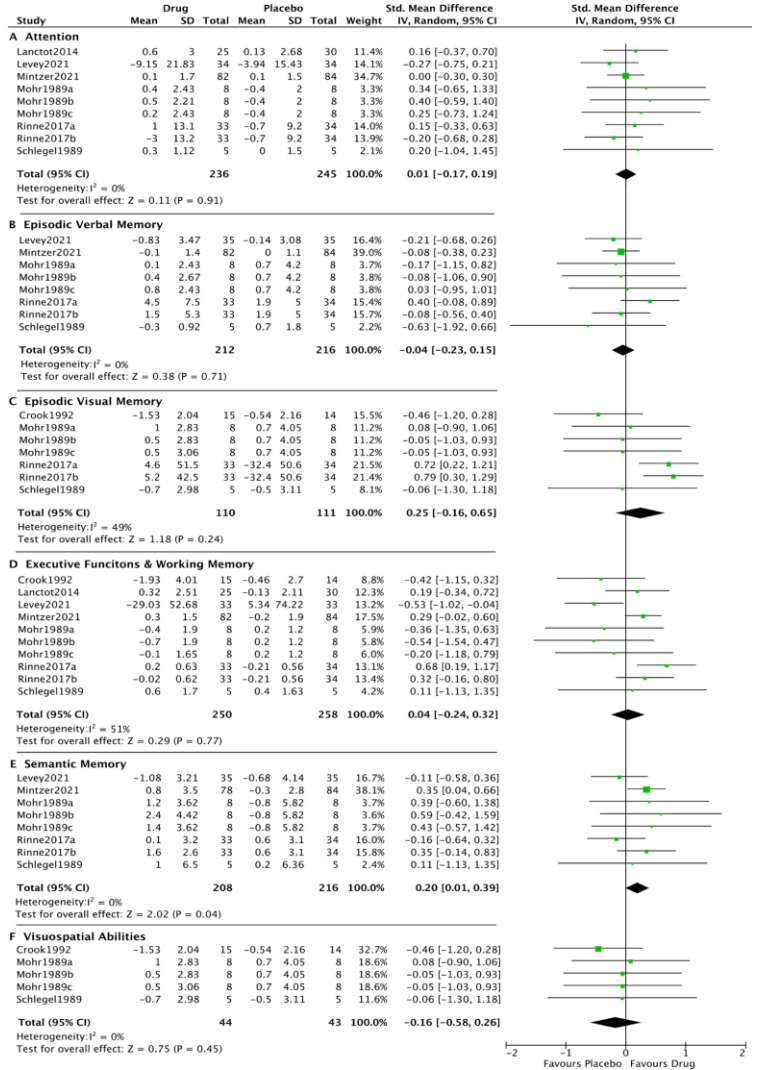
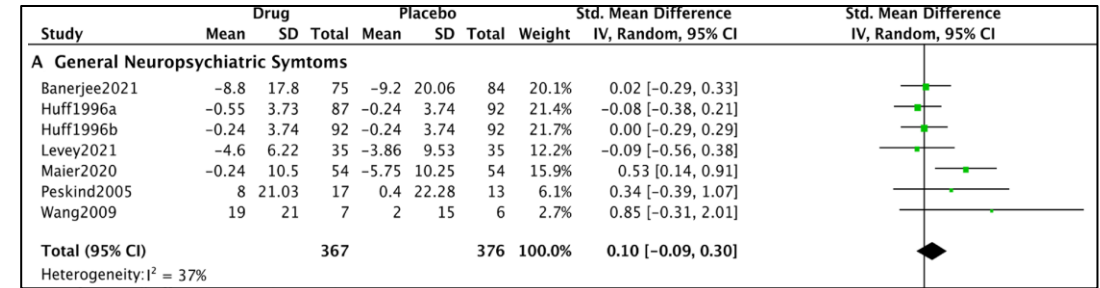
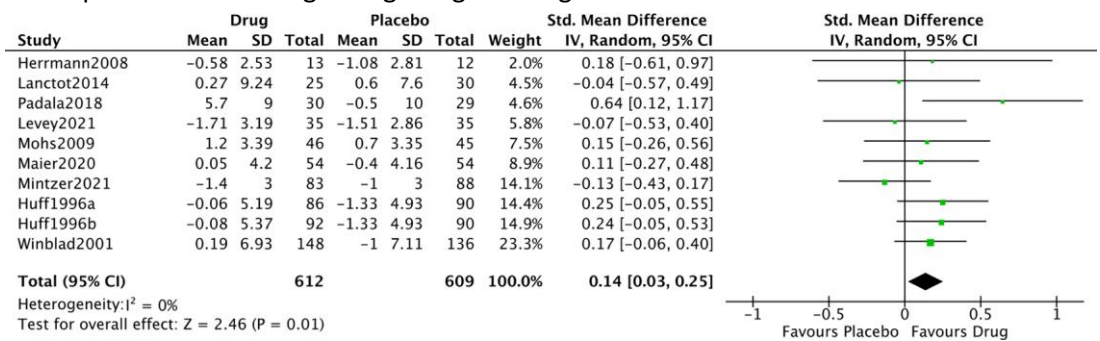
► Methylphenidates/amphetamines

- *FDA indications:* ADHD and narcolepsy
- *Off-label considerations:*
 - Inattention (moderate to severe TBI)
 - Apathy/amotivation (degenerative diseases)
 - Hyper-somnolence (DLB or AD)



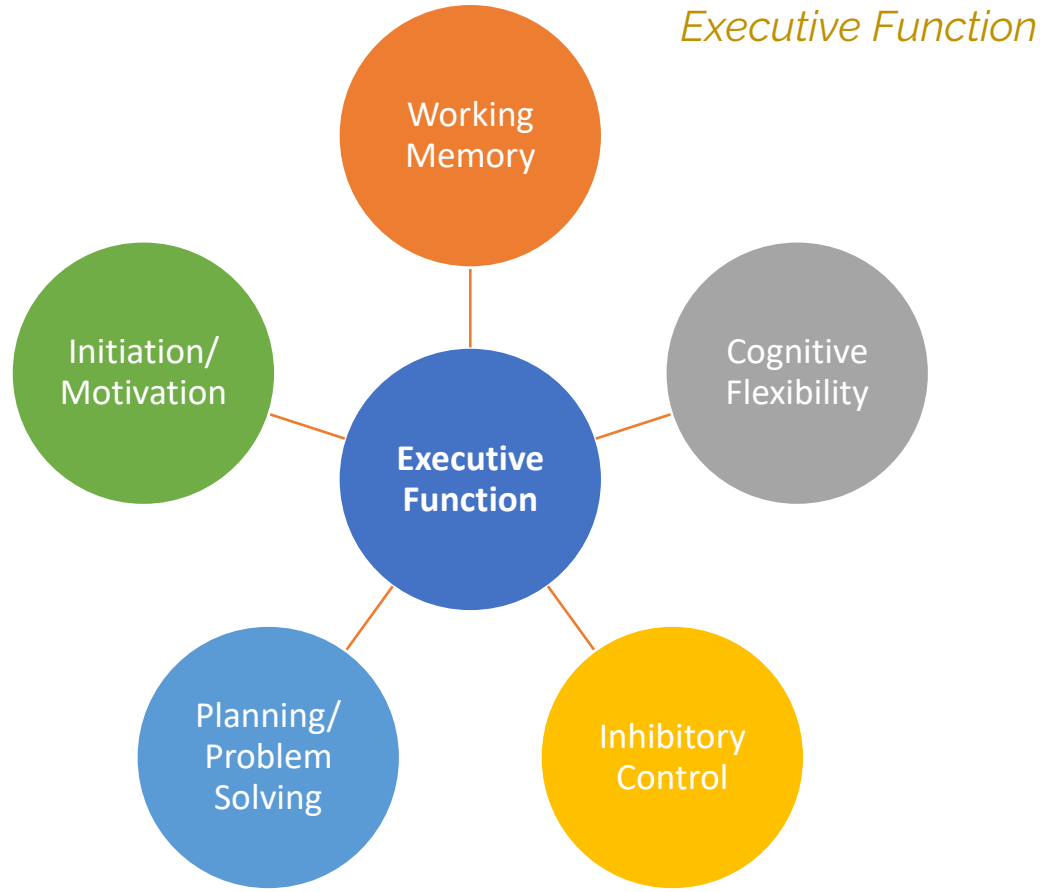
Noradrenergic treatment in Alzheimer Disease

Forest plot of noradrenergic drugs on global cognition.



Disorders of Executive Function

Background



Psychopharmacology

▶ **α 2-Adrenergic agonists**

- Improve working memory, behavioral inhibition, attention
- E.g., Clonidine, Guanfacine
- *FDA indications:* Hypertension
- *Off-label considerations:*
 - Hyperactivity/impulsivity (ADHD)
 - Behavioral disinhibition (Intellectual disabilities)
 - Agitation, inattention, restlessness (dementia)

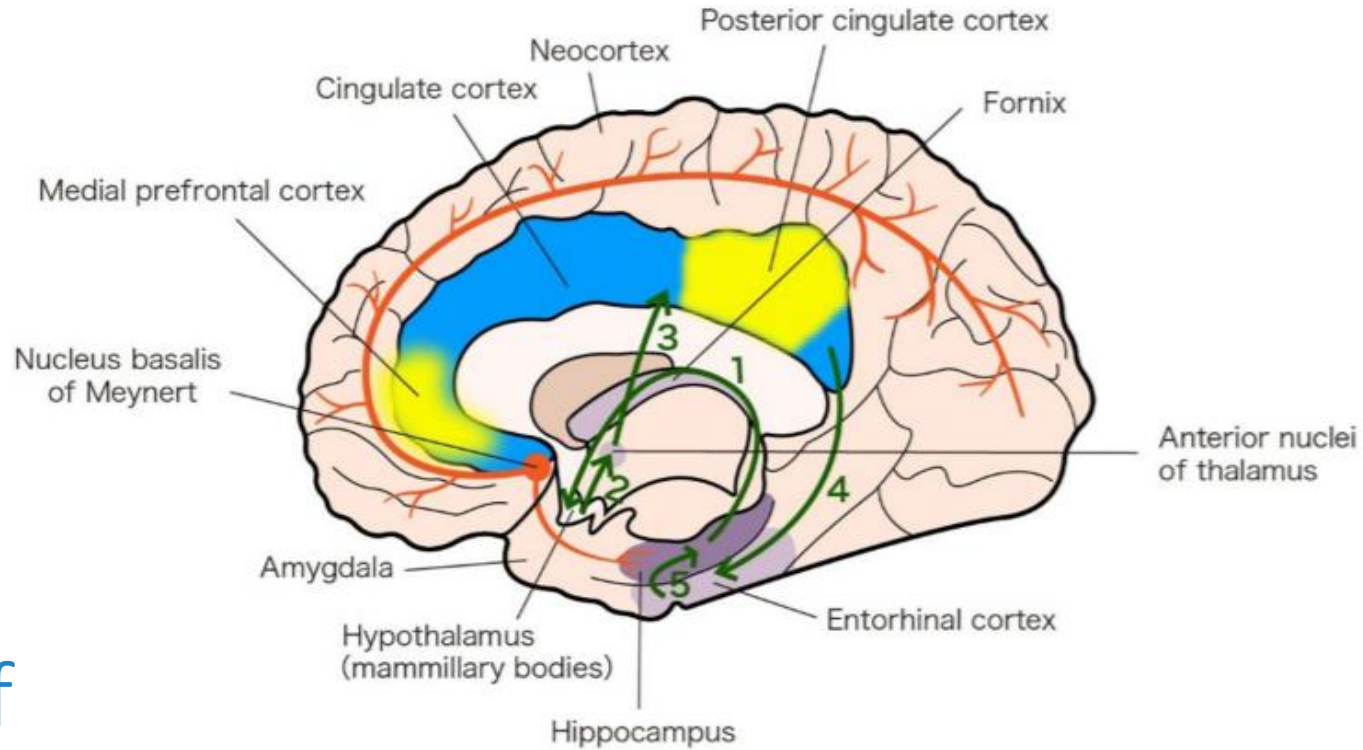
Psychopharmacology

▶ **Pramipexole, ropinirole**

Increase DA transmission in brainstem and cortical/subcortical pathways

- FDA indications: Parkinson disease, Restless leg syndrome
- Off-label considerations:
 - Apathy/executive dysfunction
 - Working memory (Parkinson) but mixed evidence

Disorders of Memory



Lv et al (2018)

Psychopharmacology

▶ Rivastigmine, galantamine, donepezil

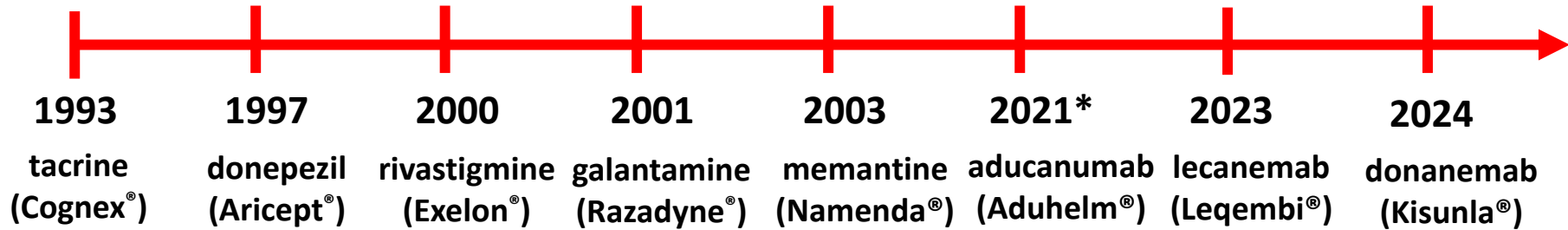
- *FDA indications:* Alzheimer's disease dementia, Parkinson disease dementia
 - Side effects: GI disturbance (switch to patch) and vivid dreams (switch to AM). Watch heartrate.
- *Off-label considerations:*
 - Chronic cognitive deficits (TBI)
 - cognitive impairment (post-stroke)
 - Fluctuations/cognition (DLB)

Psychopharmacology

▶ Memantine

- Non-competitive NMDA-receptor antagonist
- *FDA indications:* Moderate/Severe AD
- *Off-label considerations:*
 - Prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy
 - Preventing migraines

FDA Approved Medications for Alzheimer's Disease

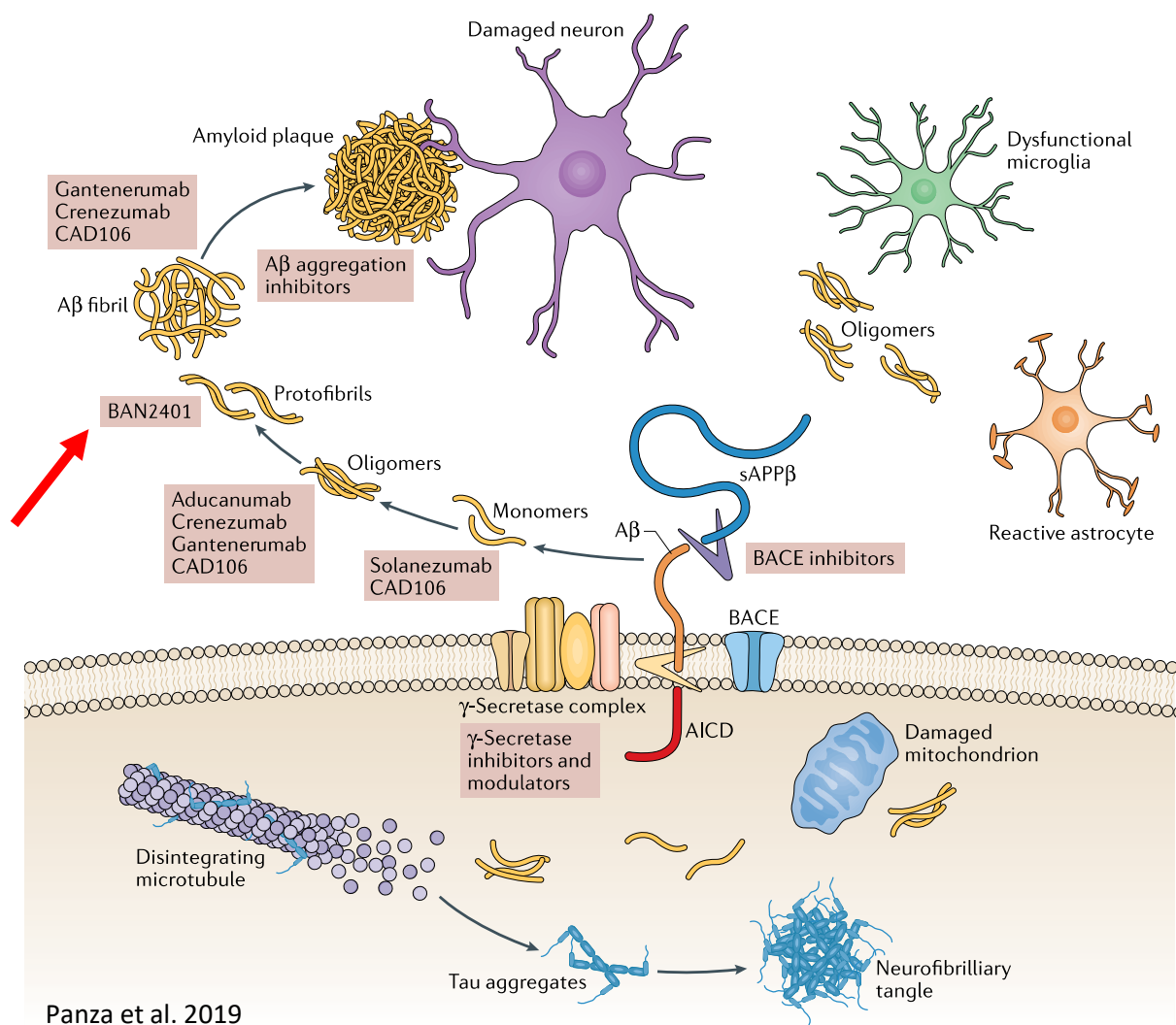


- **Cholinesterase-inhibitors (ChE-I):** donepezil, rivastigmine, galantamine, tacrine* (no longer clinically used)
 - All FDA approved for treatment of mild to moderate AD dementia
 - Donepezil also FDA approved for treatment of severe AD dementia (2006)
 - Galantamine available as a generic since 2009; donepezil, rivastigmine since 2010
 - **NMDA (glutamate) receptor antagonist:** memantine
 - FDA approved for treatment of moderate to severe AD dementia (generic 2015)
- * Accelerated approval (not traditional/full approval)

Amyloid targeting therapies for Alzheimer Disease

Lecanemab (BAN2401): Mechanism of Action

- Anti-amyloid monoclonal antibody
- Targets soluble A β oligomers and protofibrils with high selectivity (thought to be more toxic than monomers or insoluble fibrils)



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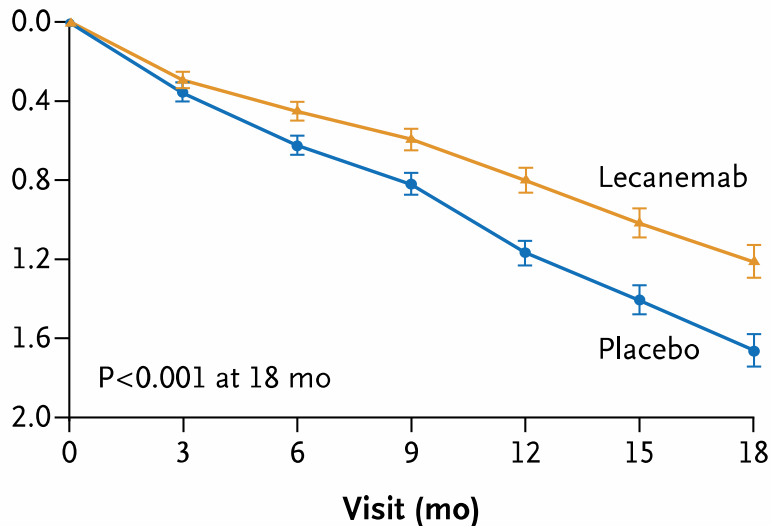
Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Worsening

Clinical Dementia Rating

Adjusted Mean Change from Baseline

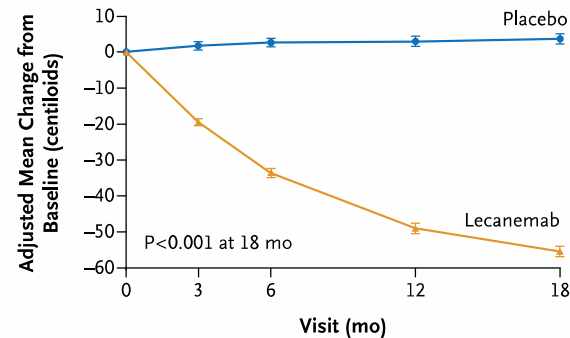


No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

B Amyloid Burden on PET

Less amyloid

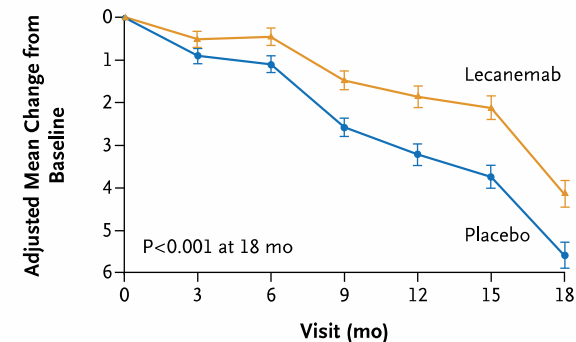


No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

C ADAS-Cog14 Score

Worsening



No. of Participants

Lecanemab	854	819	793	771	753	730	703
Placebo	872	844	823	807	770	762	738

Clarity AD: Adverse Events

Event	Lecanemab (N = 898)	Placebo (N = 897)
ARIA[‡]		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

Clarity AD: Adverse Events

Event	Lecanemab (N = 898)	Placebo (N = 897)
ARIA-H according to ApoE ϵ 4 genotype — no./total no. (%)		
ApoE ϵ 4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ϵ 4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ϵ 4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ϵ 4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

- 2.4% of anticoagulated participants developed macrohemorrhages
- 3 deaths occurred in open label extension in the context of ARIA-H or ARIA-E
 - 1 participant was anticoagulated
 - 1 participant received thrombolytic treatment for acute stroke
 - 1 participant was not anticoagulated

van Dyck et al. *N Engl J Med* 2022; Reish et al. *N Engl J Med* 2023

Donanemab in Early Symptomatic Alzheimer Disease

The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

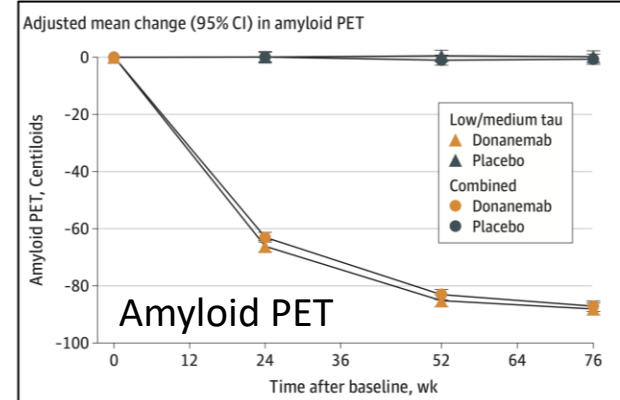
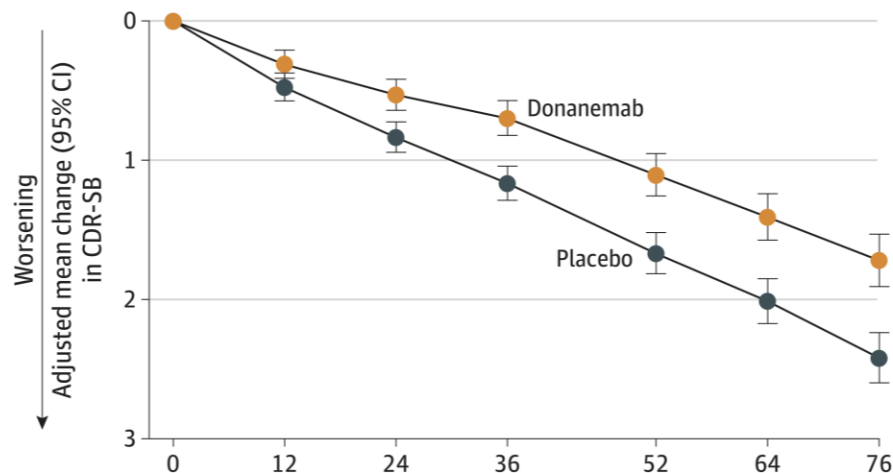
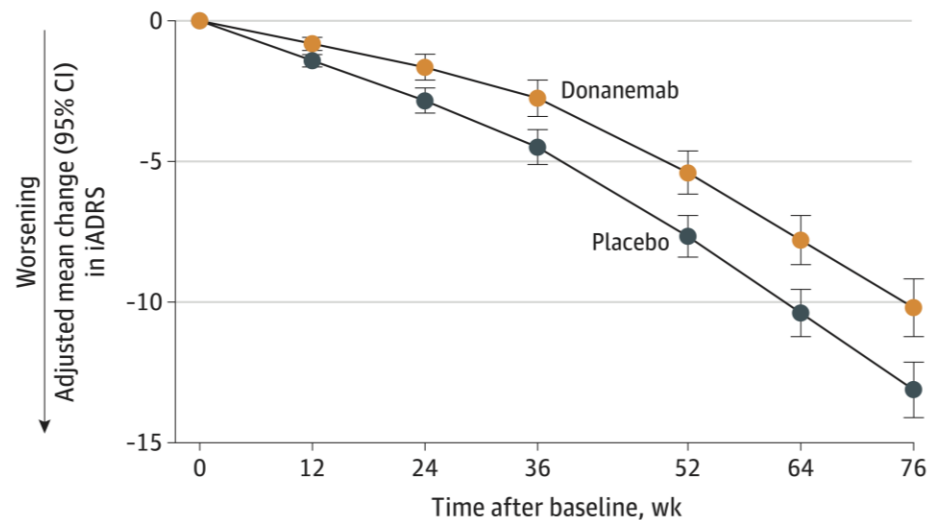


Figure 2. Integrated Alzheimer Disease Rating Scale (iADRS) and Sum of Boxes of the Clinical Dementia Rating Scale (CDR-SB) From Baseline to 76 Weeks

D CDR-SB in combined population



B iADRS in combined population



Glucagon-Like Peptide-1 (GLP-1) receptor agonists

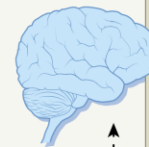
Endocrine-metabolic

- ↓ Peripheral and neural insulin resistance
- ↓ Mitochondrial function and energy metabolism
- ? HPA and other stress hormones



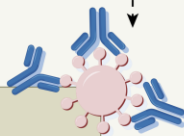
Neurobiological

- ↑ **Neuroprotection** (↑BDNF, ↑neurogenesis, ↓amyloid/tau deposits, ↓neuroinflammation)
- ~ **Neurotransmission** (5HT, DA, opioid)
- ~ **Neurometabolism** (brain glucose metabolism, mitochondrial function)
- ? **Neuropsychology** (reward, mood, memory, emotional processing, executive functioning)



Immunological

- ~ Microglia function
- ↓ BBB leak
- ↓ Peripheral inflammation and oxidative stress



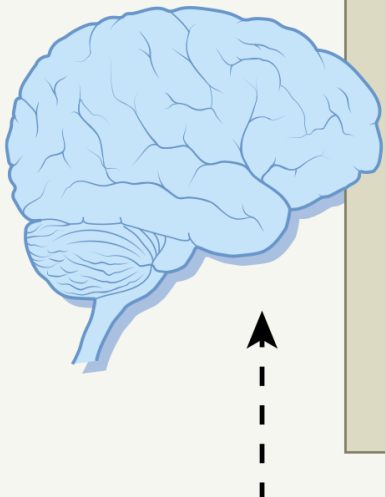
Gut-brain axis

- ↑ **Satiety** (direct, hypothalamus; indirect, GI and ~ related reward (DA))
- ? Gut microbiota protection



GLP1-RA





Neurobiological

- ↑ **Neuroprotection** (↑BDNF, ↑neurogenesis, ↓amyloid/tau deposits, ↓neuroinflammation)
- ~ **Neurotransmission** (5HT, DA, opioid)
- ~ **Neurometabolism** (brain glucose metabolism, mitochondrial function)
- ? **Neuropsychology** (reward, mood, memory, emotional processing, executive functioning)

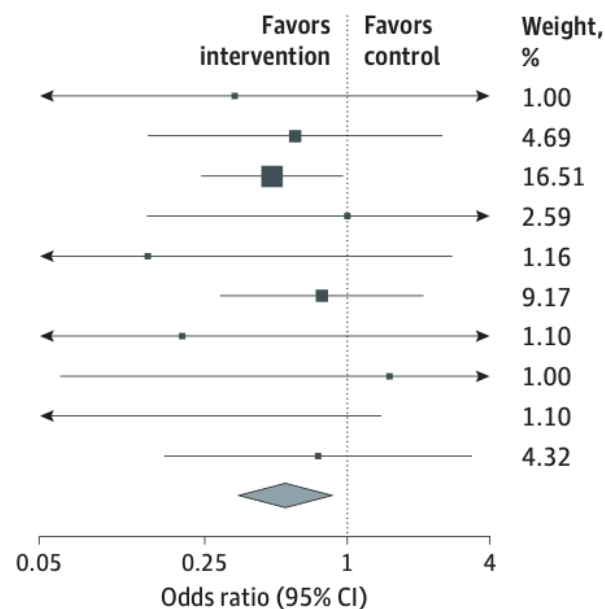
Cardioprotective Glucose-Lowering Agents and Dementia Risk

A Systematic Review and Meta-Analysis

Figure 1. Association of Glucose-Lowering Therapy With All-Cause Dementia

B GLP-1RA

Study	Intervention event	Total	Control event	Total	ARR (95% CI)	Odds ratio (95% CI)
Pfeffer et al, ³⁹ 2015	0	3034	1	3034	0.03 (-0.06 to 0.12)	0.33 (0.01 to 8.18)
Marso et al, ⁵¹ 2016	3	1648	5	1649	0.12 (-0.21 to 0.46)	0.60 (0.14 to 2.51)
Marso et al, ⁴⁰ 2016	12	4668	25	4672	0.28 (0.02 to 0.53)	0.48 (0.24 to 0.95)
Holman et al, ⁴¹ 2017	2	7356	2	7396	0.00 (-0.05 to 0.05)	1.01 (0.14 to 7.14)
Hernandez et al, ⁴⁷ 2018	0	4731	3	4732	0.06 (-0.02 to 0.15)	0.14 (0.01 to 2.77)
Gerstein et al, ⁴² 2019	7	4949	9	4952	0.04 (-0.12 to 0.20)	0.78 (0.29 to 2.09)
Husain et al, ⁴³ 2019	0	1591	2	1592	0.13 (-0.09 to 0.34)	0.20 (0.01 to 4.17)
Gerstein et al, ⁴⁴ 2021	1	2717	0	1359	-0.02 (-0.15 to 0.12)	1.50 (0.06 to 36.88)
Frias et al, ⁴⁵ 2022	0	304	2	102	2.26 (-0.74 to 5.27)	0.07 (0.00 to 1.39)
Lincoff et al, ⁴⁸ 2023	3	8803	4	8801	0.01 (-0.05 to 0.07)	0.75 (0.17 to 3.35)
RE model for subgroup: $Q = 4.72$; $df = 9$; $P = .86$; $I^2 = 0\%$					0.07 (0.02 to 0.1)	0.55 (0.35 to 0.86)



GLP-1 receptor agonists

Cognitive disorders	Positive effect	No effect	Negative effect
Meta-analyses	3	1	-
Clinical trials	3	5	1
Observational studies	8	1	-
Case series	-	-	-

GLP-1 receptor agonists

Table 1 | Clinical studies of GLP-1RAs for cognitive disorders (meta-analysis)

Study ID	Design	Population	Intervention/exposure	Comparison	Follow-up	Outcomes	Major findings
Luan 2022 ³⁸	Meta-analysis of 5 studies (5 RCTs)	7,732 adults T2DM	Dulaglutide, exenatide, liraglutide	Pre-treatment baseline	3 months–5 years	MMSE, MoCA	SMD=0.33 = 95% CI=−0.03, 0.69 (P=0.017)
Nørgaard 2022 ³⁹	Pooled analysis of 3 RCTs	15,820 adults T2DM	Liraglutide, semaglutide	Placebo	1.3–3.8 years	Risk of any dementia	HR=0.47 + 95% CI=0.25, 0.86
Tang 2023 ⁴⁰	Meta-analysis of 4 studies (1 pooled analysis of 3 RCTs, 3 observational studies)	210,521 adults T2DM	Any GLP-1RAs	Non-users of GLP-1RAs	3.6–7.4 years	Risk of any dementia	RR=0.72 + 95% CI=0.54, 0.97 (P=0.000)
Tian 2023 ⁴¹	Network meta-analysis of 27 studies (4 for GLP-1RAs: 1 RCT, 3 case-control studies)	149,560 adults T2DM	Dulaglutide, exenatide, liraglutide	Non-users of GLP-1RAs	4–7.2 years	Risk of any dementia	OR=0.34 + 95% CI=0.14, 0.85 (P=0.021)

Plus and equals symbols indicate positive effect and no effect, respectively. Values are mean±s.d. unless otherwise specified. Study ID reports the first author and year only. CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk; SMD, standardized mean difference.

GLP-1 receptor agonists

- A meta-analysis of 5 RCTs comprising 7,732 adults with T2DM did not observe any effect on cognition, as measured via mini-mental state examination (MMSE) or Montreal cognitive assessment (MoCA), of GLP-1RAs over several months compared with the baseline.
- A pooled analysis of 3 longer-term RCTs following 15,820 patients with T2DM up to 3.8 years showed a reduced risk of dementia for semaglutide and liraglutide compared with placebo. The same paper also included a nested case-control component of 120,054 patients with T2DM followed for 7.4 years and observed a lower association between dementia and exposure to GLP-1RAs compared with other antidiabetics. This finding was further supported when pooled with further observational data to a total of 210,521 people with T2DM up to 7.4 years on any GLP-1RA.
- Four RCTs in Parkinson's disease looking at both motor and non-motor outcomes, but results were inconsistent depending on the different scales used within the same trial; overall, one showed a more beneficial profile, while the other three did not find any consistently positive effect.

Nootropics

Nootropics are “cognitive enhancers”

Apoaequorin (Prevagen) – purported to act like calmodulin

- A total of 218 participants, ages 40 to 91, with self-reported memory concerns were enrolled in the 90-day study. Study is posted on company website but does not seem to have undergone peer review.
- Non-standard memory tests were employed with a reported benefit in cognition compared to placebo. Not clear how many participants had MCI or AD
- **“This product is not intended to diagnose, treat, cure or prevent any disease.”**

Medications with cognitive side effects

ANTICHOLINERGICS

Antihistamines

Diphenhydramine
Hydroxyzine

Antidepressants

TCAs
SSRIs (paroxetine)

Antimuscarinics

Oxybutynin

Antipsychotics

Typical and atypical

Antiparkinsonian

Benzotropine
Trihexyphenidyl

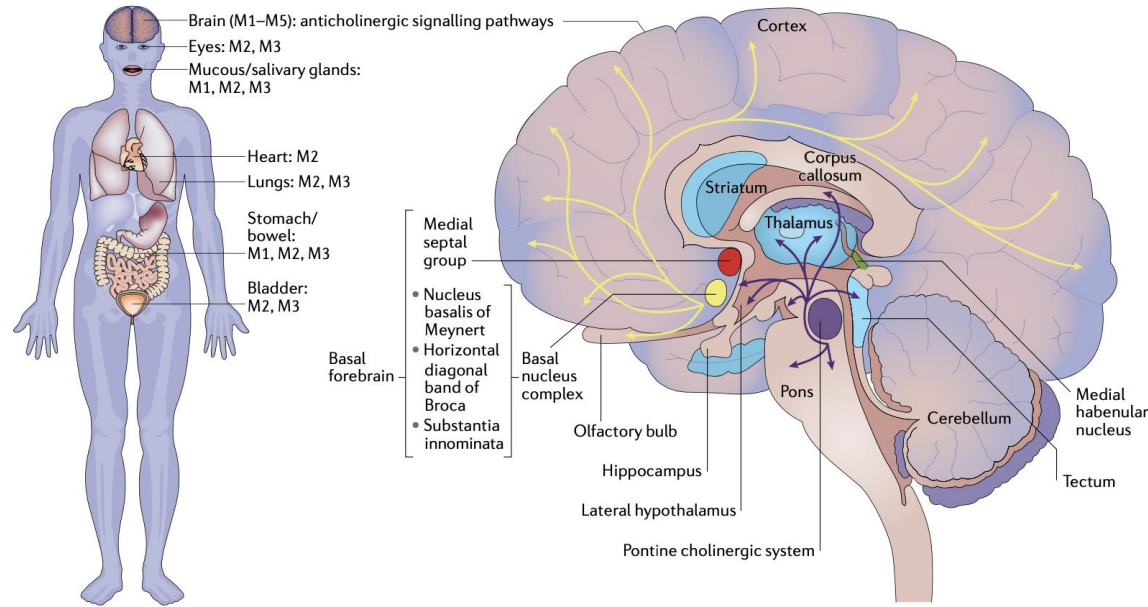
Skeletal muscle relaxants

Cyclobenzaprine

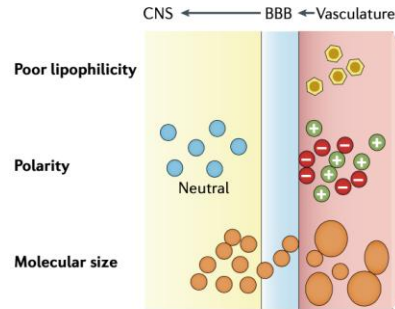
Antispasmodics

Loperamide

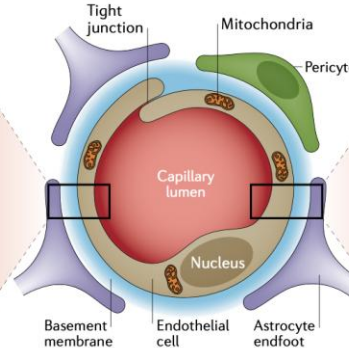
Differential impact of anti-cholinergic bladder medications on cognitive function



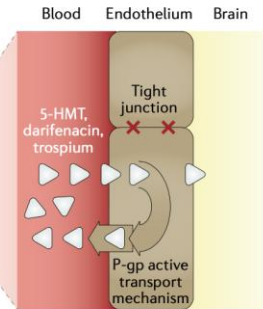
Physicochemical characteristics of OAB medications that influence passive diffusion across the BBB



Anatomy of the BBB



Active transport mechanism



A systematic review of neurocognitive dysfunction with overactive bladder medications

Vi Duong¹  • Aya Iwamoto² • Jon Pennycuff³ • Bela Kudish⁴ • Cheryl Iglesia³

Received: 3 March 2021 / Accepted: 25 May 2021 / Published online: 2 July 2021
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Abstract

Introduction and hypothesis The aim of this study is to report cognitive dysfunction with commonly used antimuscarinic overactive bladder medications in patients suffering from overactive bladder disorder with and without baseline neurologic conditions.

Methods We conducted an Ovid MEDLINE, Embase, and PsycINFO search from January 1998 to December 2018 using PRISMA guidelines. Eighteen studies met the inclusion criteria, including 5 randomized controlled trials and 13 observational studies.

Results Cognitive decline was reported with oxybutynin use (5 of 8 studies) and tolterodine use (4 of 7 studies) among patients with and without baseline cognitive impairment. Oxybutynin use was linked to functional, mental, and behavioral decline among patients with Alzheimer’s disease (2 studies). No cognitive decline was detected among patients with and without baseline cognitive impairment taking trospium (6 studies), darifenacin (3 studies), imidafenacin (2 studies), and fesoterodine (1 study). Solifenacin was not associated with cognitive decline (2 studies) but was linked to an increased risk of dementia among patients with diabetes (1 study).

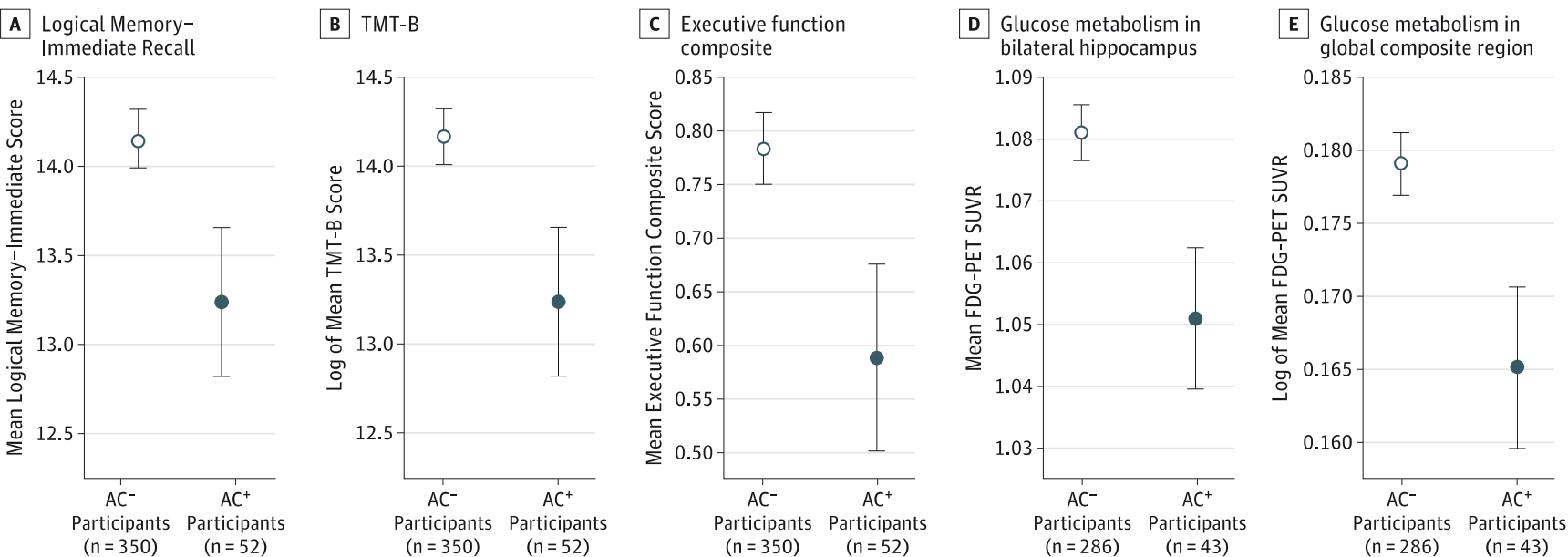
Conclusion In this review, cognitive decline was reported with oxybutynin and tolterodine use and should be used with caution in adults over 65 years of age. Solifenacin, fesoterodine, and imidafenacin showed mixed results related to central nervous system effect. Trospium and darifenacin were not associated with cognitive decline among patients with and without baseline cognitive impairment.

Trospium: Of the six studies that investigated trospium use, **no cognitive decline was detected among overactive bladder patients with and without baseline cognitive impairment.**

Physiologically one study showed that use of extended release trospium chloride 60 mg daily for 10 days was undetectable in cerebrospinal fluid samples.

Concurrently, there was no decline in performance on tests of memory and recall detected before and after trospium administration.

Figure 1. Association of Anticholinergic (AC) Medication Use With Cognition and Glucose Metabolism Among Participants From the Alzheimer’s Disease Neuroimaging Initiative (ADNI)



Cognitively normal older adults taking 1 or more medications with medium or high AC activity (referred to as AC+ participants [n = 52]) showed poorer cognition than those not taking these medications (referred to as AC– participants [n = 350]), including a lower score on the Weschler Memory Scale–Revised Logical Memory Immediate Recall (P = .04 [A]), the Trail Making Test Part B (TMT-B) (P = .04 [B]), and an executive function composite (P = .04, with transient ischemic attack, myocardial infarction, and diabetes as additional covariates [C]). Glucose hypometabolism, as measured by the fluorodeoxyglucose F 18–positron emission tomographic (FDG-PET) standardized uptake value ratio (SUVR), was also observed in the bilateral hippocampus (P = .02, with anxiety as an additional covariate [D]) and in a global cortical region of interest of AC+ participants (n = 43) relative to AC– participants (n = 286), generated from an analysis of cognitively normal participants who show greater glucose metabolism than participants with AD from the full ADNI 1 cohort (P = .03, with other vascular conditions and concussion as additional covariates [E]). Error bars indicate SD. (JAMA Neurol. 2016;73(6):721-732. doi:10.1001/jamaneurol.2016.0580)

Second-Generation H1-Antihistamines Do Not Alter Dementia Risk in Type 2 Inflammatory Diseases: A Target Trial Emulation Using Real-World Data

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What is already known about this topic? Second-generation H1-antihistamines (sgAHs) are widely used and considered safe. Previous observational studies have raised concerns about a possible association between AH use and dementia risk.

What does this article add to our knowledge? In a large real-world target trial emulation, sgAH use was not associated with increased dementia risk. Lower dementia rates in patients with allergic rhinitis treated with intranasal corticosteroids, compared with those treated with sgAHs, might be associated with a protective effect of the former rather than the harmful effects of the latter.

How does this study impact current management guidelines? The findings support continued use of sgAHs without dementia concerns and reinforce intranasal corticosteroids as the preferred treatment for allergic rhinitis when indicated.

CONCLUSION: Overall, our findings do not support increased dementia risk associated with 2nd generation antihistamine use. Lower dementia rates in patients with acute rhinitis treated with corticosteroids might be associated with the protective effects of corticosteroids rather than the harmful effects of sgAHs. (Intranasal steroids use in patients with AR was associated with a slight decrease in dementia risk ($P < 0.007$))

Medications with cognitive side effects

OTHER MECHANISMS

Barbiturates

Butalbital
Primidone

Non- benzodiazepine hypnotics

Zolpidem

Benzodiazepines

Antiepileptic drugs

Topiramate

Calcium channel blockers(?)

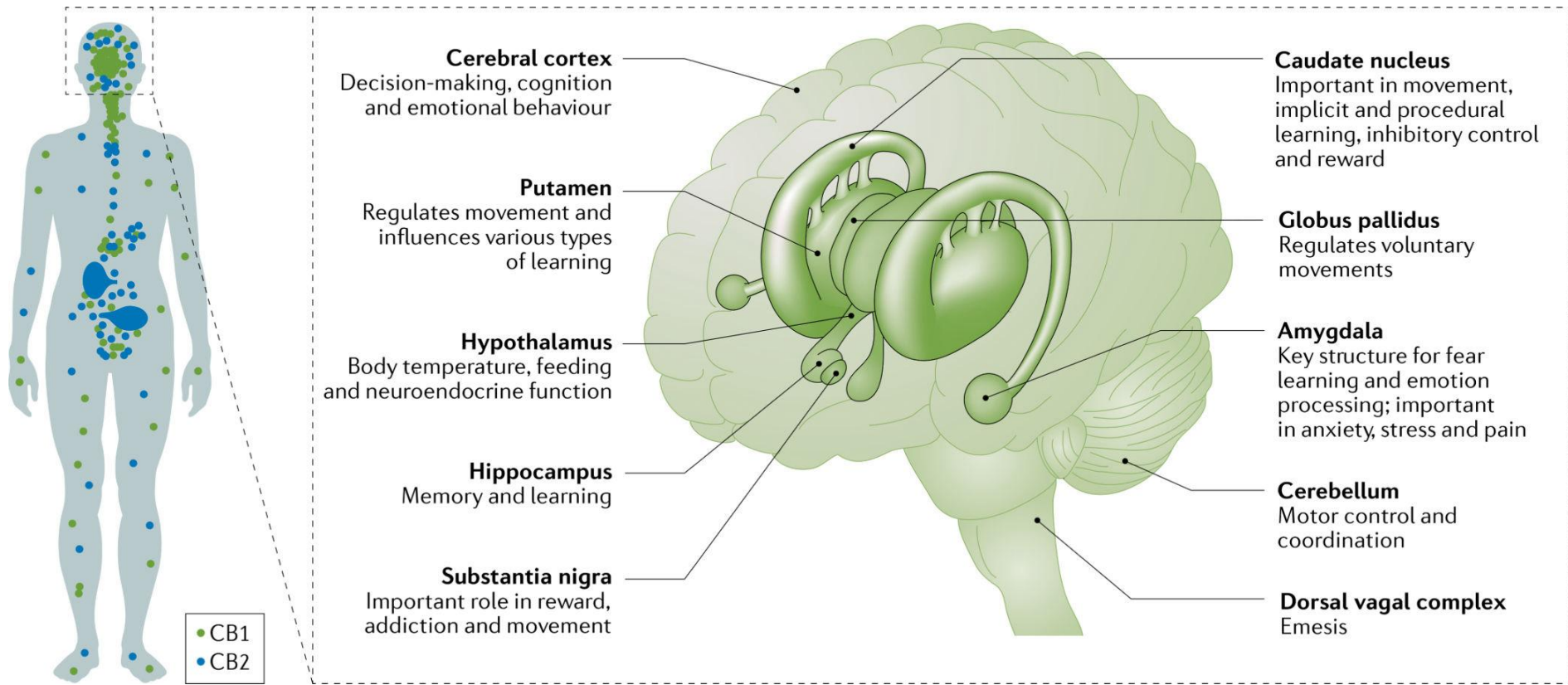
Amlodipine
Nifedipine

Pain medications

Narcotics

Corticosteroids

Sulfonamides



Distribution of cannabinoid CB1 and CB2 receptors

Cannabis

Cannabis

- Evidence of acute impairment of learning and memory, attentional control, motor inhibition and emotion processing
- Magnitude of impairment/persistence may depend on the frequency and duration of use, length of abstinence, and age of onset
- Decrease motivation/apathy

Table 1. Strength and Consistency of Evidence for Impairment Associated With Acute and Chronic Cannabis Use and for Recovery of Function With Abstinence From Research Published in the Past Decade^a

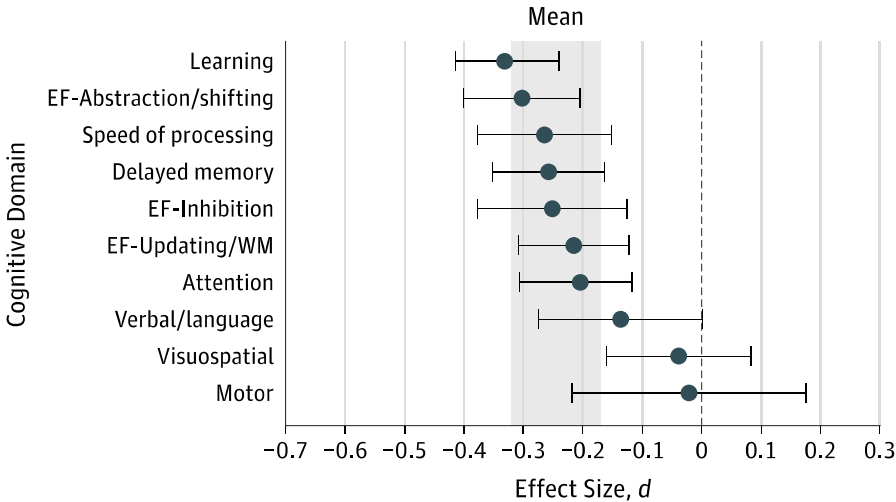
Cognitive Domain	Acute ^b	Chronic ^b	Persistence With Abstinence ^b	Pertinent Cannabis Use Parameters	Number of Studies		
					Acute	Chronic	Abstinence
Memory							
Verbal learning and memory	+++	+++	+-	Frequency; lifetime use; duration; age of onset; sex	11 (36-44,77,87)	20 (44-58,60-62,66,142)	9 (55,57,60,63-67,95)
Working memory	+-	+-	+-	Frequency; lifetime use; recency; sex	20 (36-40,42,43,68-78,88,143)	16 (46,48,49,51-53,55,57,79-84,115,119)	7 (55,57,64,65,67,79,85)
Other memory function	+	+-	-	Age of onset; frequency; recency	2 (42,144)	8 (45,49,78-80,119,144,145)	4 (63,65,79,95)
Attention							
Attention	+++	+++	+-	Dose; age of onset; length of abstinence; withdrawal effects	16 (36,37,39,42,43,68,70,71,76,77,86-90,143)	14 (45,46,54,55,57,61,79-81,84,91-94)	10 (55,57,63,64,67,79,91-93,95)
Attentional bias	+	+++	NA	Craving; dependence; frequency; CBD	1 (102)	7 (96-102)	None
Psychomotor Function	+++	+	+		18 (37,42,43,68,70,73,74,76,77,89,90,103-107,143,146)	10 (46,48,51,54,57,66,78,80,91,108)	6 (57,63-65,67,91)
Executive Function							
Planning, reasoning, interference control, and problem solving	+-	+-	+-	Neurodevelopmental stage; age of onset; frequency	12 (37-41,77,86,89,103,104,106,109)	23 (46,48,52-54,57,60,61,66,78,81-84,93,98,110-115,147)	9 (57,60,63-65,67,85,93,95)
Inhibition	++	+-	NA	Frequency; task complexity	5 (42,89,103,104,109)	9 (45,50,54,56,82,110,116-118)	None
Verbal fluency	-	+-	+-		3 (36,38,44)	6 (44,48,51,53,54,61)	4 (65,67,93,119)
Time estimation	+-	-	-		6 (73,74,77,86,148,149)	1 (55)	1 (55)
Decision Making	+-	+-	-	Age of onset; lifetime exposure; frequency; cannabis use disorder	7 (103,105,106,109,120-122)	17 (45,48,50,56,78,82,84,94,113,116,117,123-126,128,150)	3 (85,127,128)

CBD, cannabidiol; NA, not available (not investigated).

^aThe prevalence of studies focused on acute vs. chronic effects is unequal, as is the focus on individual cognitive domains; strength metrics are based on qualitative interpretation of the literature, subjectively weighed on greater or lesser evidence for impairment across the published studies, considering the number of studies conducted and their quality (e.g., design, sample size), reached by consensus between the authors of this review.

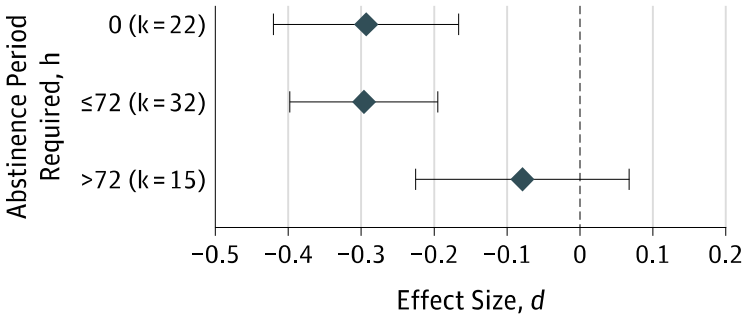
^b+++ , strong and largely consistent evidence for impairment; ++ , moderate evidence for impairment; + , weak evidence for impairment, being based on only a small number of studies; +- , mixed evidence; - , little or no evidence for impairment.

Figure 2. Mean Weighted Effect Sizes for Each Neurocognitive Test Domain

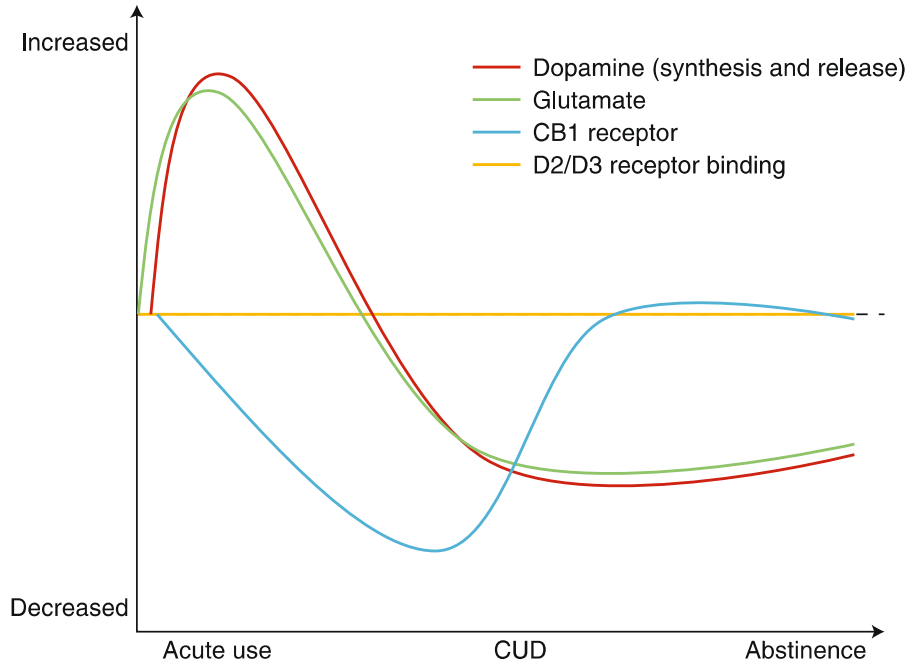


The mean value shown is the grand mean effect size of 69 included studies; d is the standardized mean difference. The shaded area indicates the 95% CI around the mean, -0.247 . EF indicates executive functioning; SIP, speed of information processing; WM, working memory. Blue circles indicate the domain effect size d ; gray bands, the overall means; error bars, 95% CIs.

Figure 3. Mean Weighted Effect Sizes for Varying Abstinence Criteria



Subgroup analyses compared effect sizes (standardized mean difference d) from studies with abstinence periods longer than 72 hours to effect sizes from studies with abstinence lengths equal to or less than 72 hours. Data from all 3 groups are presented here to show that the subgroup of studies with unknown or 0 abstinence are not the primary contributor to reported subgroup differences. Blue diamonds indicate the domain effect size d ; error bars, 95% CIs.

a

Line graphs indicate specific alterations during acute use as compared to neurobiological state in individuals with cannabinoid use disorder, including during periods of abstinence.

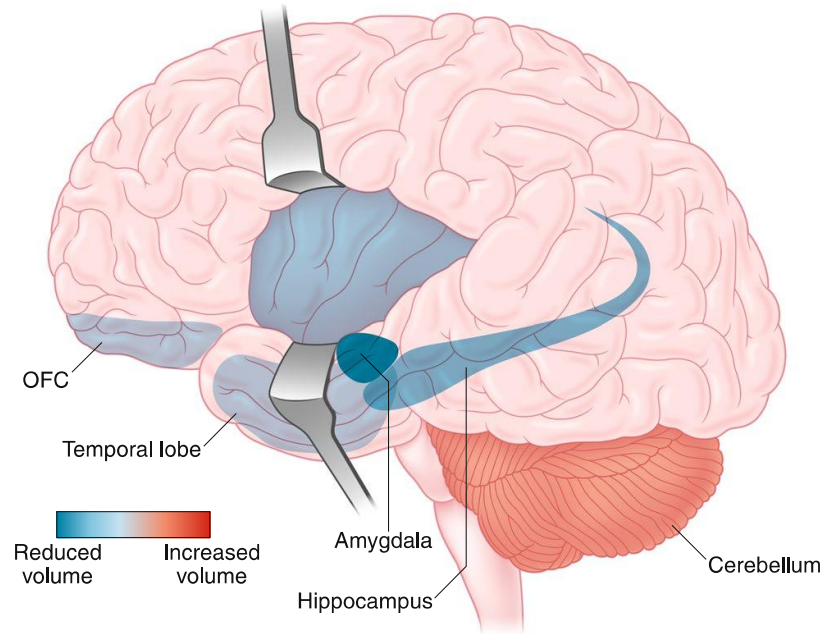
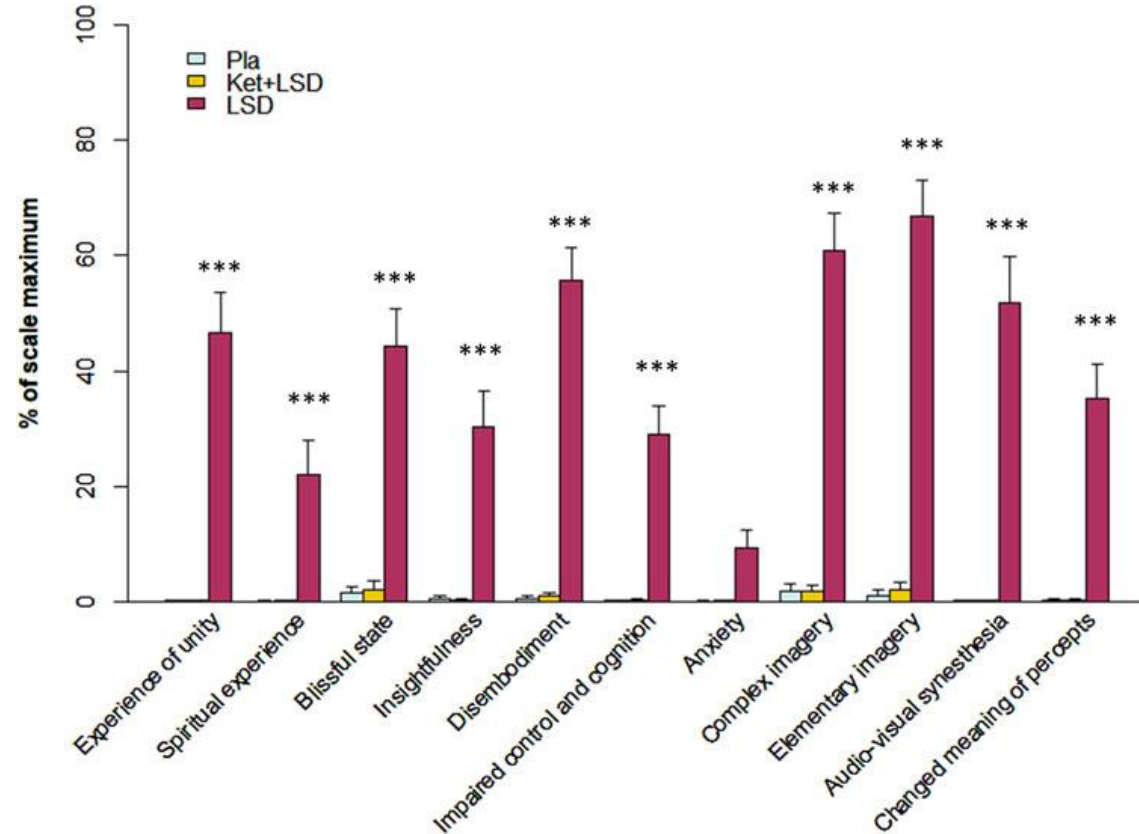


Fig. 3 | Alterations of gray matter volume (based on MRI studies) detected in individuals with CUD. Colors denote decreased (red) and increased (blue) gray matter volume. Illustrator: Debbie Maizels/ Springer Nature.

Psychedelics - Serotonin: LSD

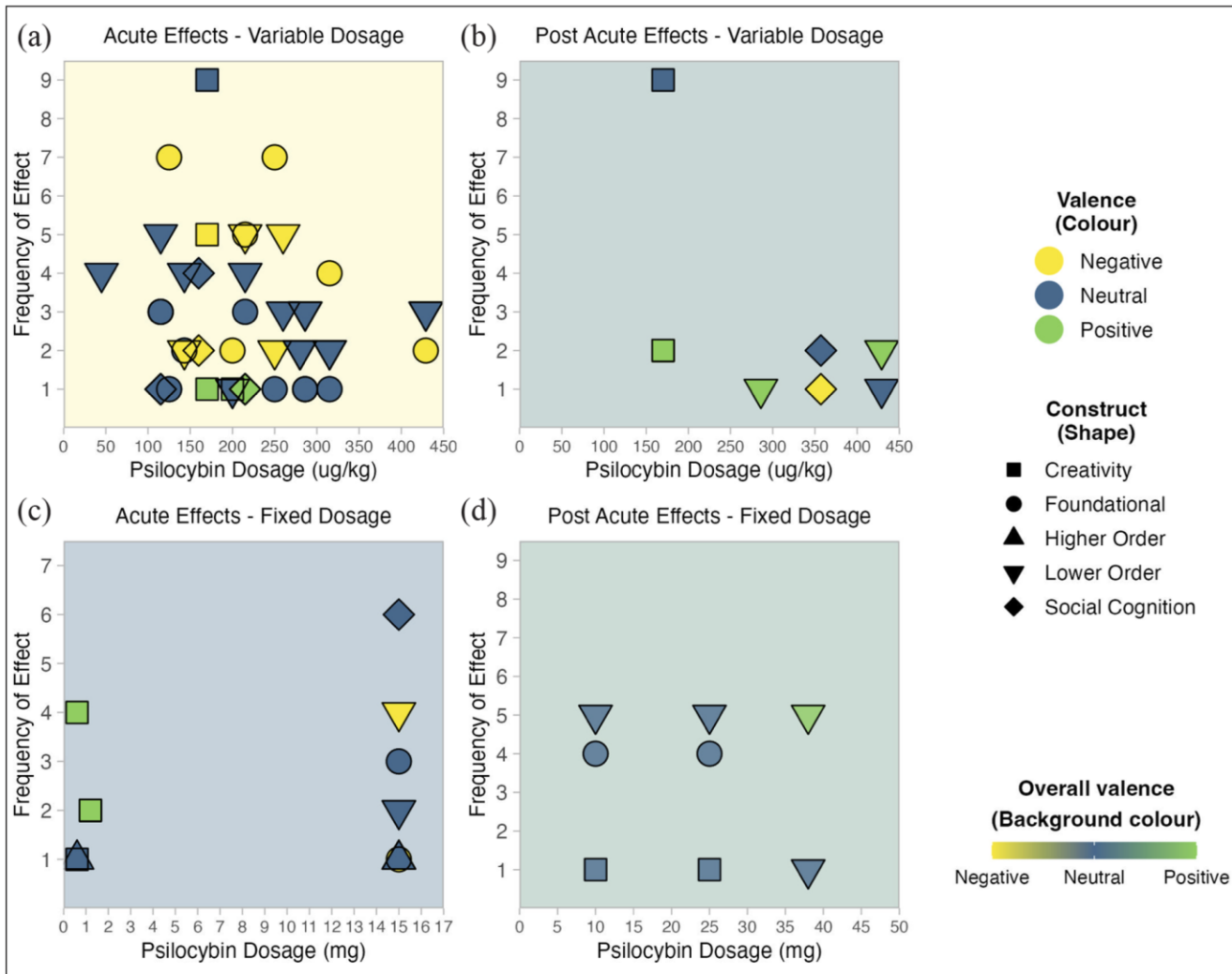
Methods. acute effects of LSD (100 µg) alone and in combination with the 5-HT_{2A} antagonist ketanserin (40 mg) on cognition, employing a double-blind, randomized, placebo-controlled, within-subject design in 25 healthy participants. Executive functions, cognitive flexibility, spatial working memory, and risk-based decision-making were examined by the Intra/Extra-Dimensional shift task (IED), Spatial Working Memory task (SWM), and Cambridge Gambling Task (CGT) of the Cambridge Neuropsychological Test Automated Battery.

Results. Compared to placebo, **LSD significantly impaired executive functions, cognitive flexibility, and working memory** on the IED and SWM, but did not influence the quality of decision-making and risk taking on the CGT. Pretreatment with the 5-HT_{2A} antagonist ketanserin normalized all LSD-induced cognitive deficits.



Subjective drug effects assessed with the 5D-ASC questionnaire 720 min after, the second, substance administration. LSD significantly increased all scale scores compared to Pla and Ket + LSD (all $p < 0.0001$, corrected), except for anxiety ($p > 0.7$, corrected). Ket = 5-HT_{2A} antagonist ketanserin

Psilocybin's effects on cognition and creativity: A scoping review

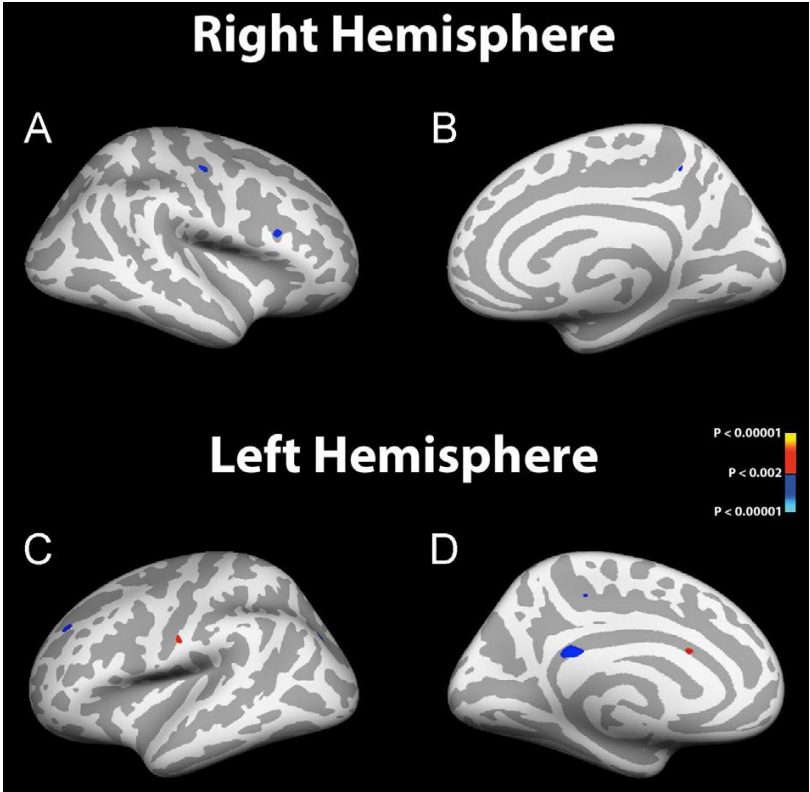


Cumulative & Descriptive Statistics of Long-term Psychedelic Studies

Year		Population		Drug	
Mean	2016	Depression	10	Psilocybin	
Median	2016	Healthy	9	LSD	
		End-of-life Distress	7	Ayahuasca	
		Tobacco Addiction	4		
		Spiritually Active	2		
		Alcoholism	1		
		Meditators	1		

Sample Size		Control		Long-term Follow-up Measures	
Mean	16.81	Yes	15	Personality/Attitude	14
		No	19	Depression	10
				Spirituality	10
				Wellbeing/QoL	9
				Anxiety	8
				Affect/Mood	7
				Qualitative Analysis	4
				Tobacco Consumption	3
				Alcohol Consumption	1
				Mindfulness	1
				Neuroimaging	1
				Meditative Practices	1

Chronic ayahuasca users showed significant cortical thickness differences in midline structures of the brain, with thinning in the posterior cingulate cortex (PCC). Values in the PCC were inversely correlated with the intensity and duration of prior use of ayahuasca and with scores on self-transcendence, transpersonal feelings and spirituality.



Review by neurotransmitter/medication target

- Noradrenaline
 - Wakefulness, vigilance, attention, anxiety
 - Role in cognition
 - Benefit in ADD and neurodegenerative disease
- Acetylcholine
 - Attention
 - Acetylcholinesterase inhibitors
 - Anticholinergics
- GABA
 - Benzodiazepines
- Cannabinoid
 - Endocannabinoids and role in memory
- Serotonin
 - LSD and psilocybin

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