DEPRESSION, ANXIETY AND DEMENTIA – THE DARK TRIAD

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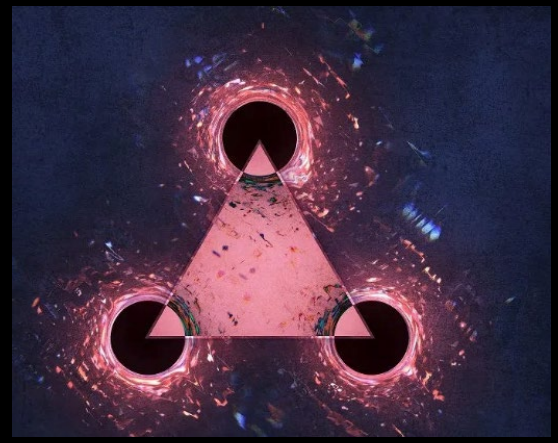
Conflict of interest/Disclosure

- Funding received from NIMH, NIA and the Goode Family Foundation

Outline

- The Dark Triad
- Late-life depression
  - Treatment response markers in men and women
  - Relapse risk in late-life
- Late-life anxiety:
  - Epidemiology Overview
  - Links with cognitive decline and differences in women and men

THE DARK TRIAD



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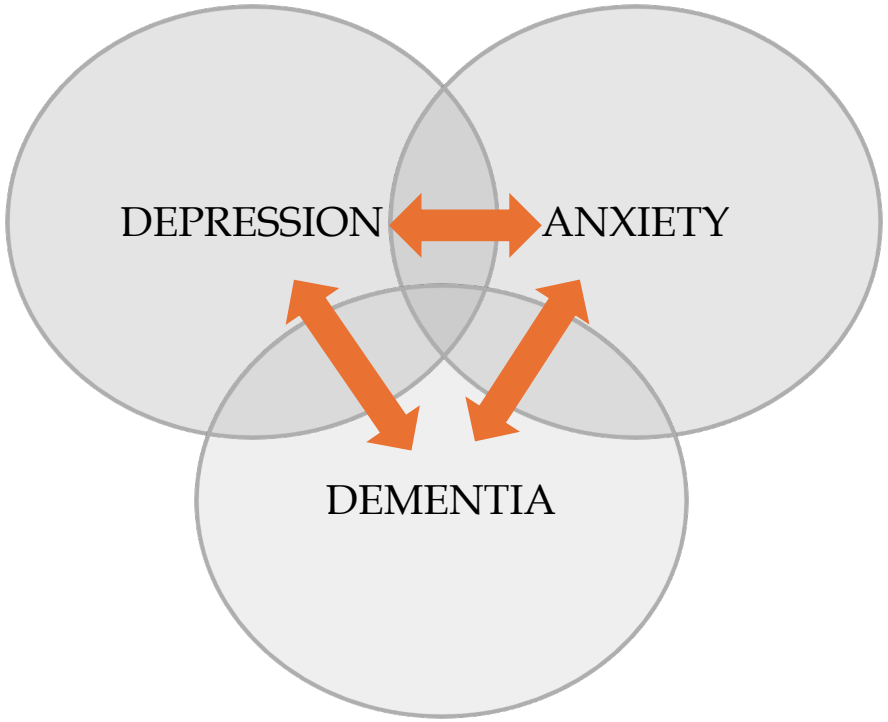

Late-life depression

- Highly recurrent
- Increased disability and mortality
- Significant socioeconomic burden
- Continued exposure to LLD - risk of metabolic diseases, cognitive decline, suicide
- **Perimenopausal women (especially racially and ethnically minoritized) – have a higher proportion of depressive symptoms**

!

- Acute treatment is only moderately effective
- Less than half of individuals respond to first-line treatment options
- Half of remitted LLD will recur within FOUR years
- Most of those will recur within the first TWO years

Taylor WD, N Engl J Med, 2014; 371: 1228-1236

Andreescu et al, Am J Geriatr Psych, 2019; 27 (12); 1316-1330

Lewis Johnson et al, J Womens Health, 2024; 33 (2): 113-131

Can we know early on who will respond to treatment?

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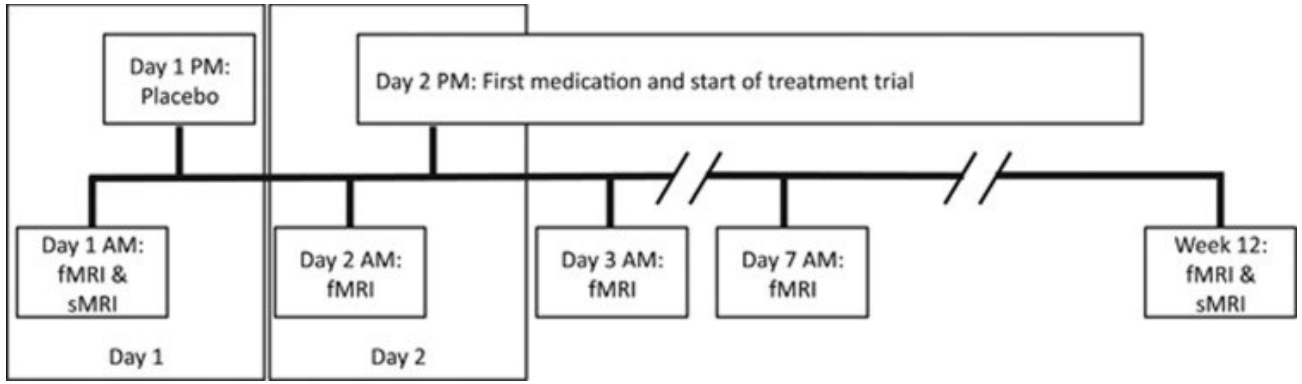
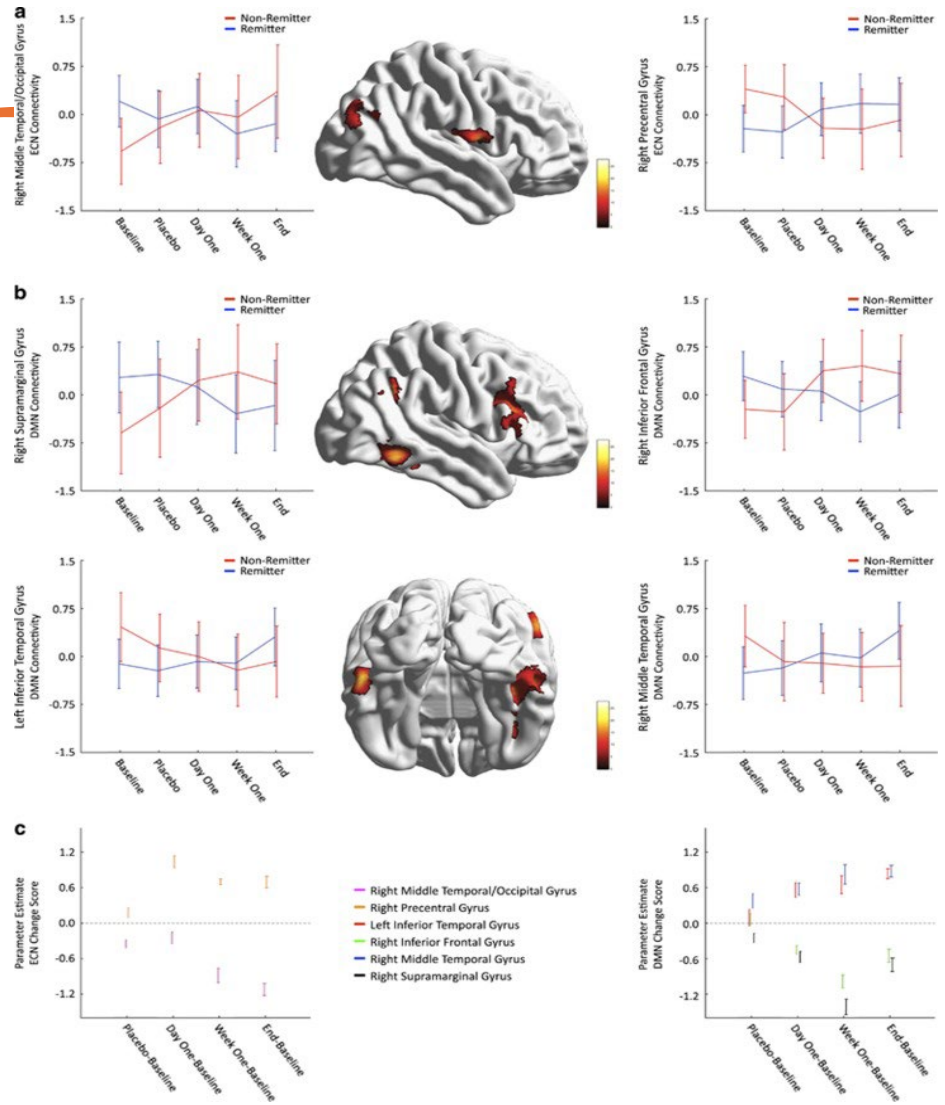
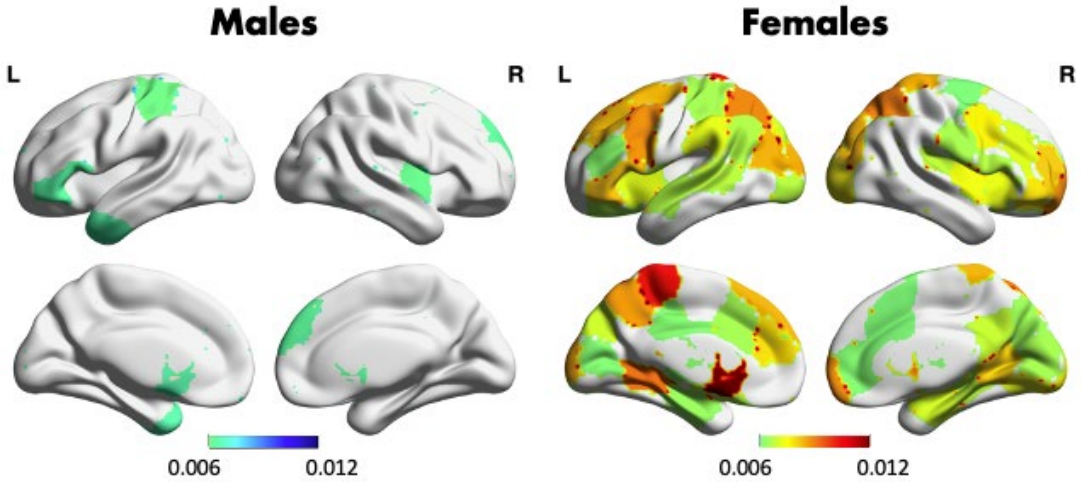




Karim et al, Mol Psychiatry, 2017

Functional Networks in Late-Life Depression – Sex matters

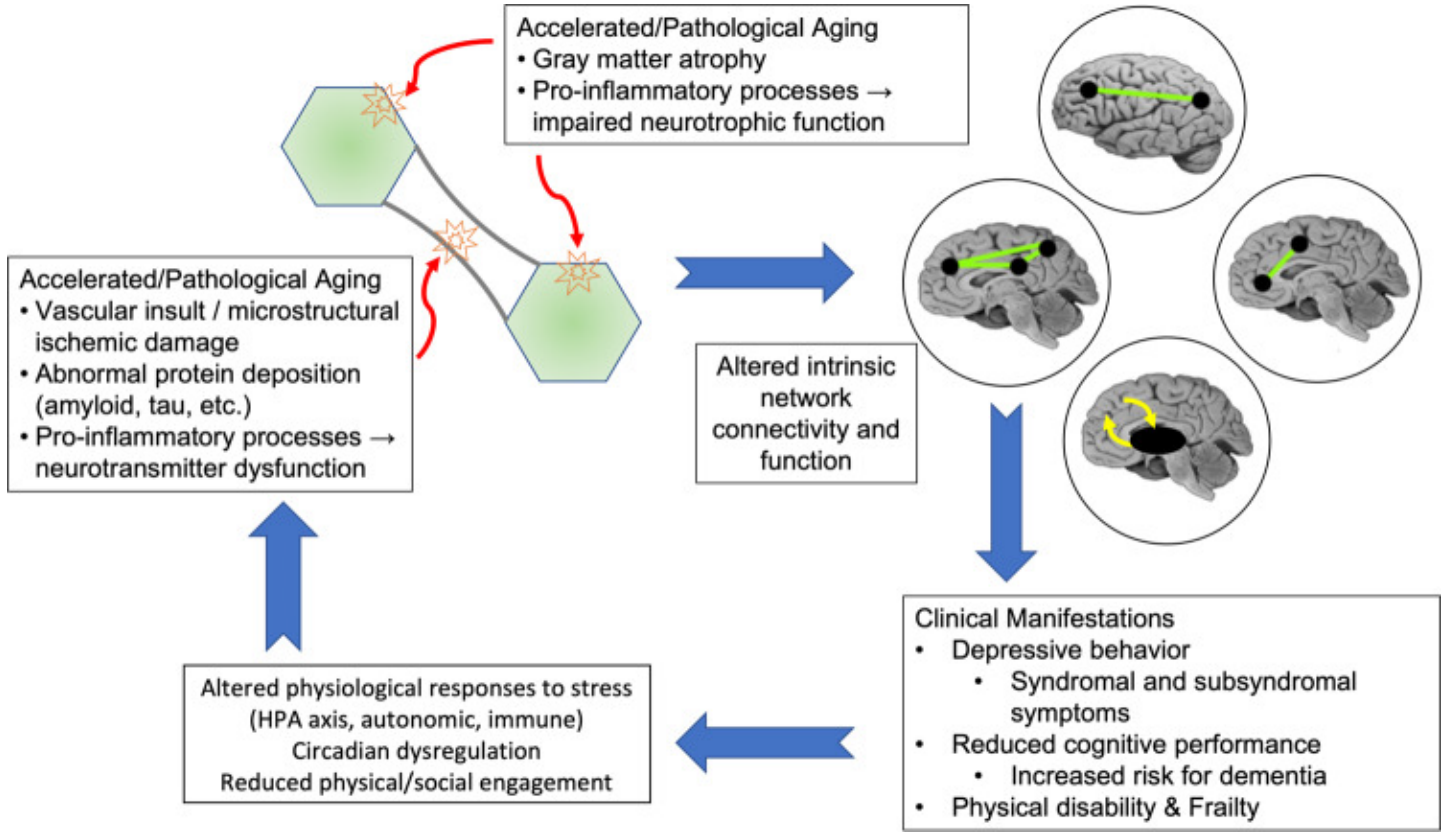
- One Day Changes in Functional Connectivity could predict treatment response in males but not in females
- Men and women recruit different nodes in the early stages of successful treatment
- For women, Salience Network Dynamics were key for remission
- For men, the interplay between Reward and Executive Control was the remission marker

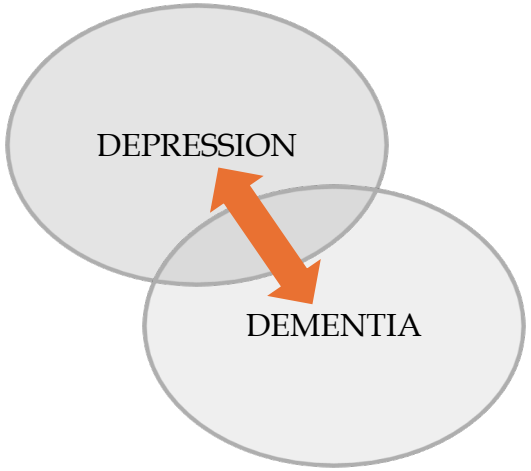


Gerlach et al, Molecular Psychiatry 2023, Jul 6:10

Late-life Depression and Cognitive Decline

- LLD is often associated with cognitive impairment
- Cognitive deficits persist with successful treatment
- Remitted LLD have an accelerated cognitive decline
- Bidirectional relationship





Taylor WD, N Engl J Med, 2014; 371: 1228-1236

Szymkowicz et al, Transl Psychiatry, 2023, 13:160

Recurrence Risk

- Acute treatment is only moderately effective
- Less than half of individuals respond to first-line treatment options
- **Half of remitted LLD will recur within FOUR years**
- **Most of those will recur within the first TWO years**

- Clinical and Behavioral Predictors
  - Number of previous episodes
  - Severity of residual depressive symptoms (anxiety, sleep, low mood)
  - Lack of maintenance treatment/poor adherence
  - Cognitive impairment
  - Medical morbidity
  - Lack of social support
  - Environmental stressors
  - Greater perceived stress
- Neurobiological Predictors

Recurrence Risk

- Acute treatment is only moderately effective
- Less than half of individuals respond to first-line treatment options
- **Half of remitted LLD will recur within FOUR years**
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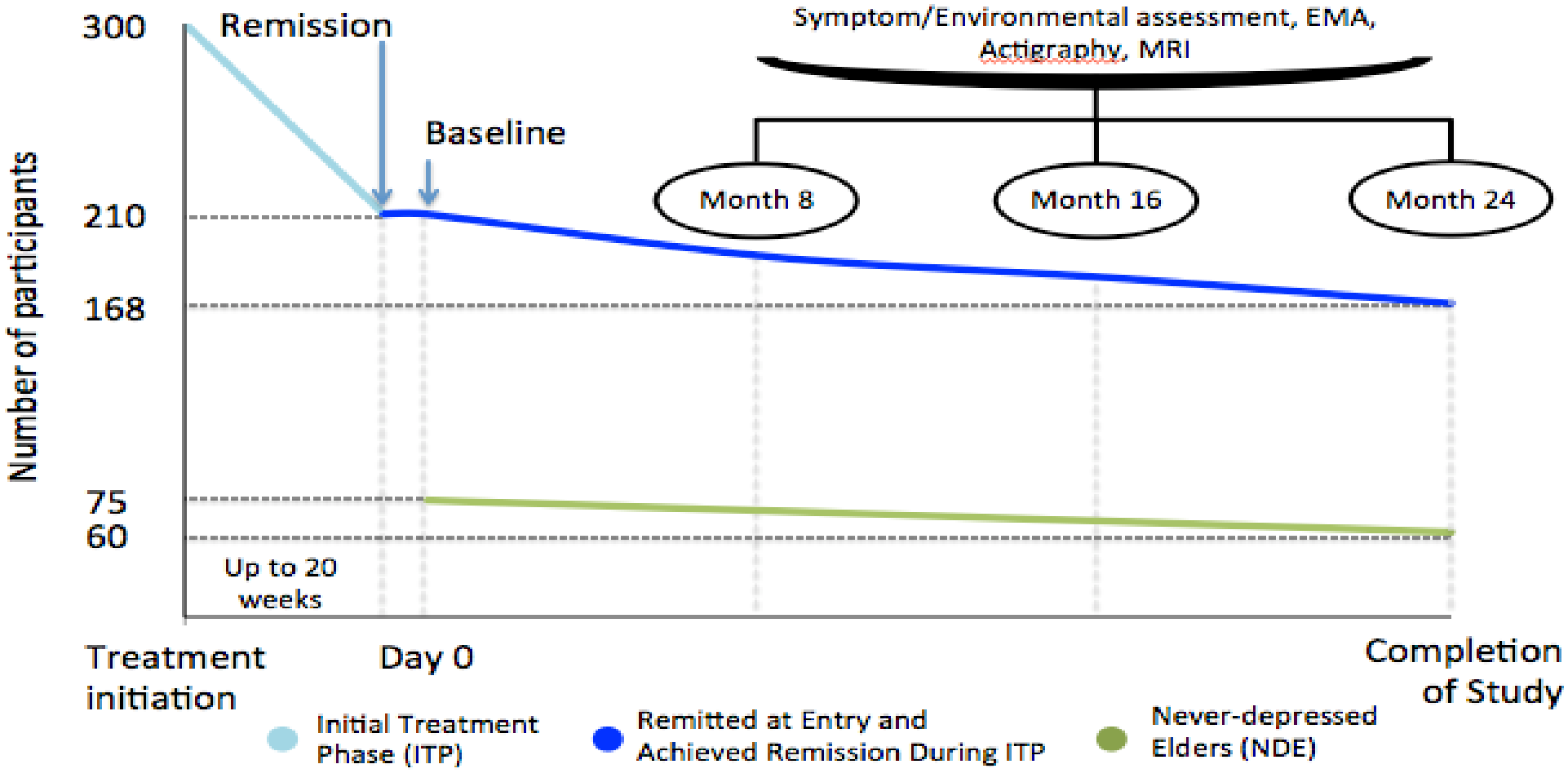
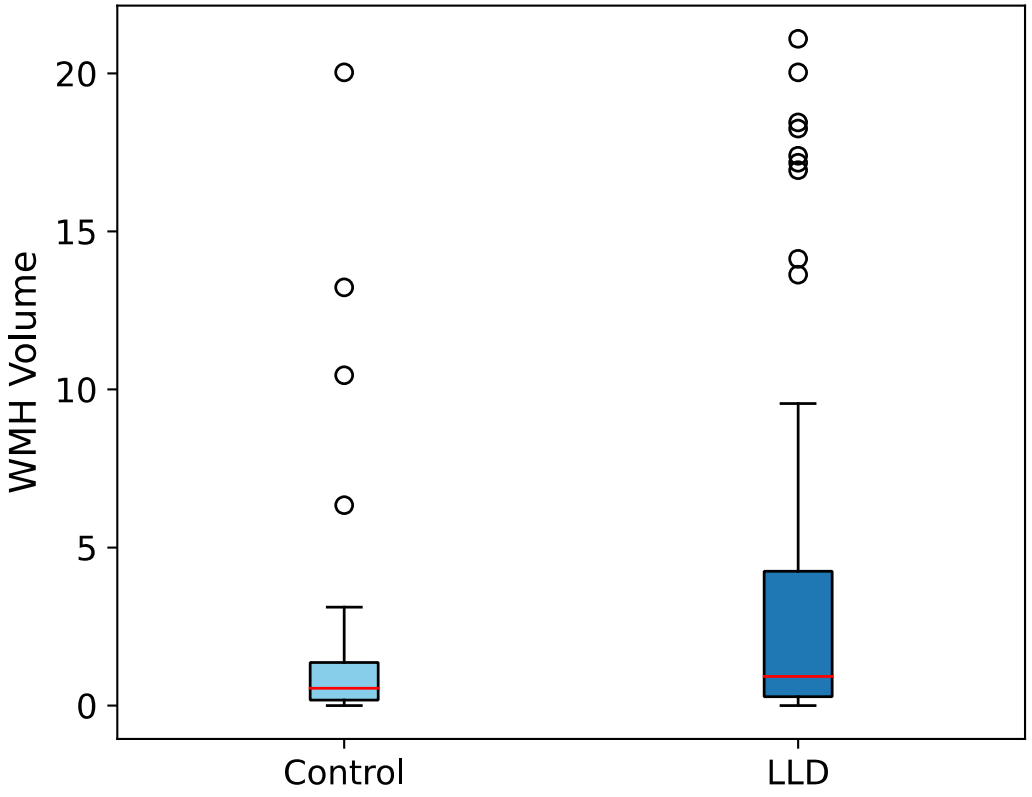
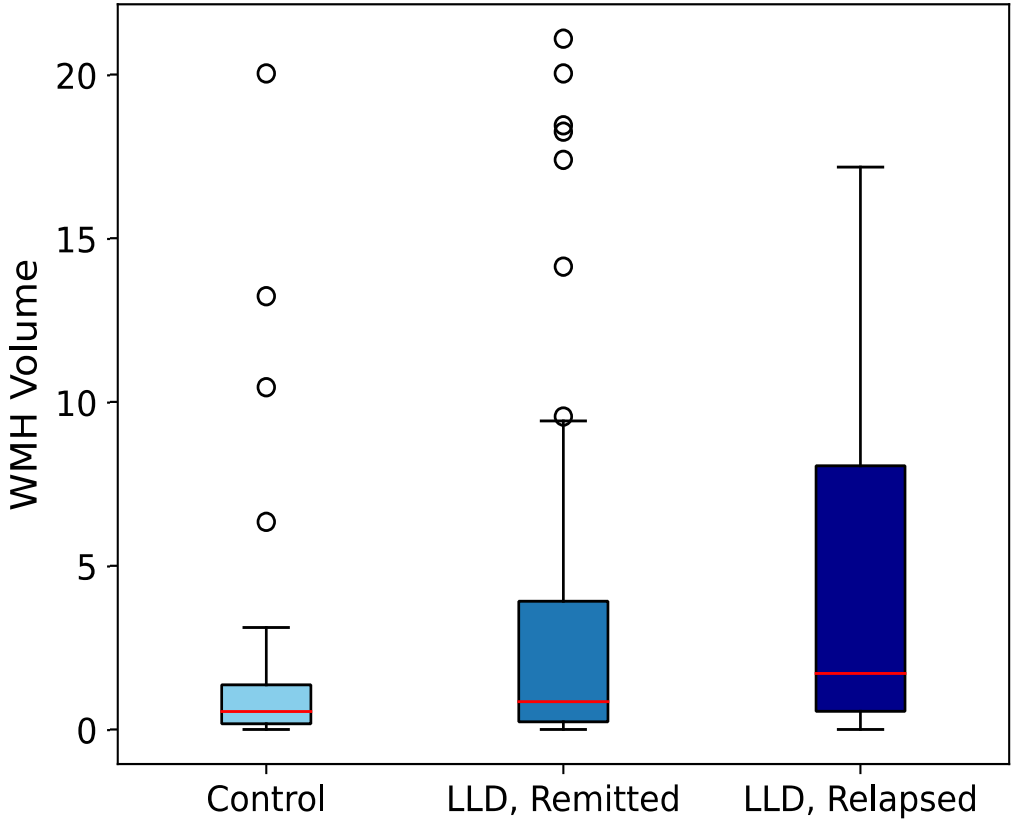
- Clinical and Behavioral Predictors
- Neurobiological Predictors
  - Greater white matter hyperintensity volumes
  - Smaller hippocampal volumes
  - DMN connectivity
  - Residual alterations in networks activity/connectivity:
    - Reduced global efficiency
    - Lower DMN deactivation during cognitive tasks*
    - Lower within-ECN connectivity during cold cognitive task*
    - Higher SN/Insula activity *
    - *In midlife cohorts

Recurrence markers, cognitive burden and neurobiological homeostasis in late-life depression (Rembrandt)



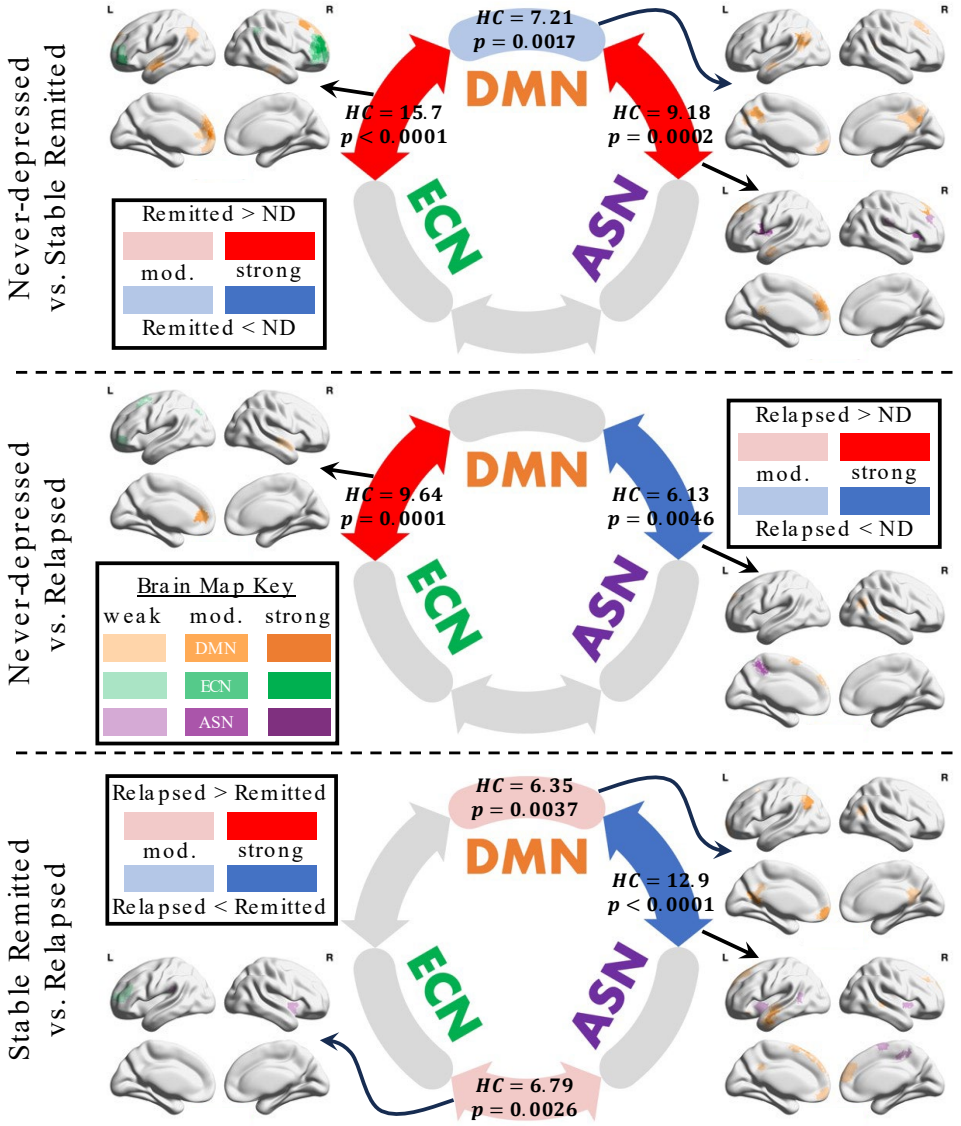
Rembrandt - Depressed vs. HC – Baseline White Matter Hyperintensities





Percy et al, in prep

Rembrandt - Resting State Connectivity at Baseline



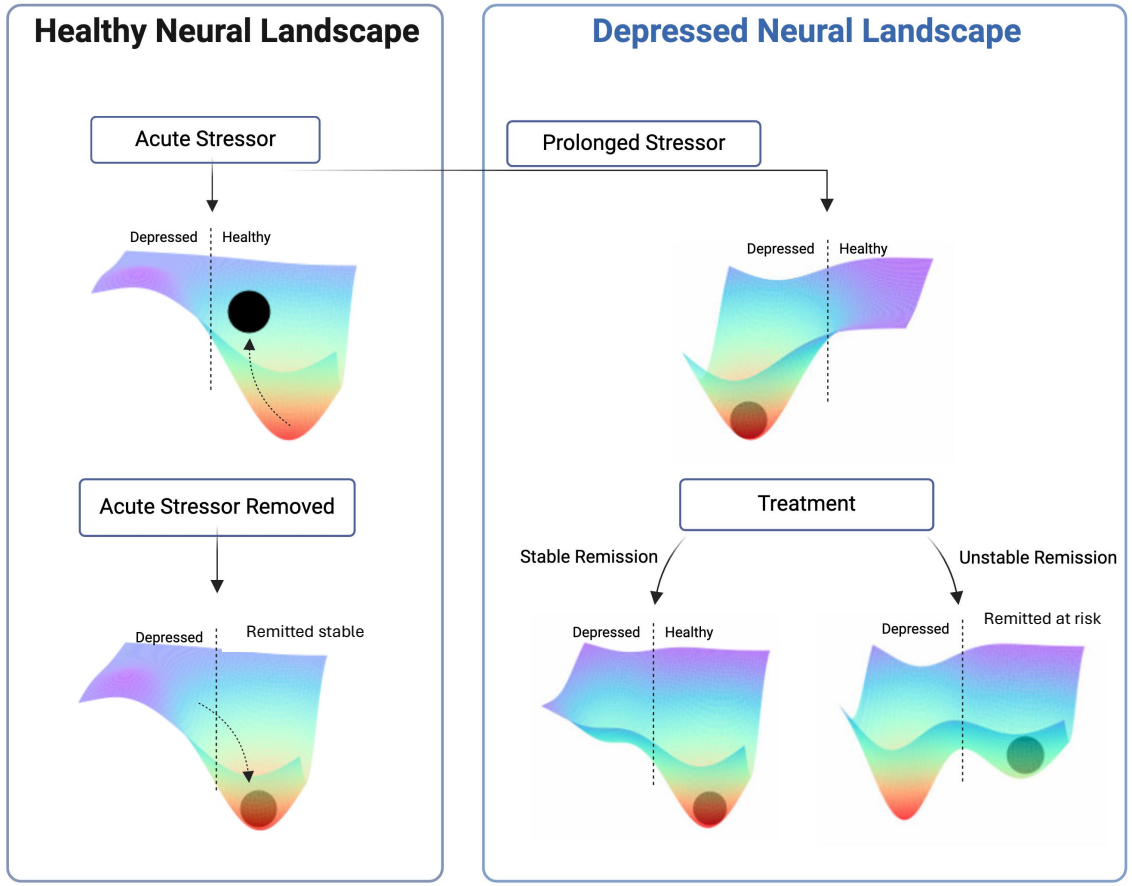
- 103 LLD remitted at baseline/72 remained remitted
- 43 controls age, race, education matched

Gerlach et al, submitted

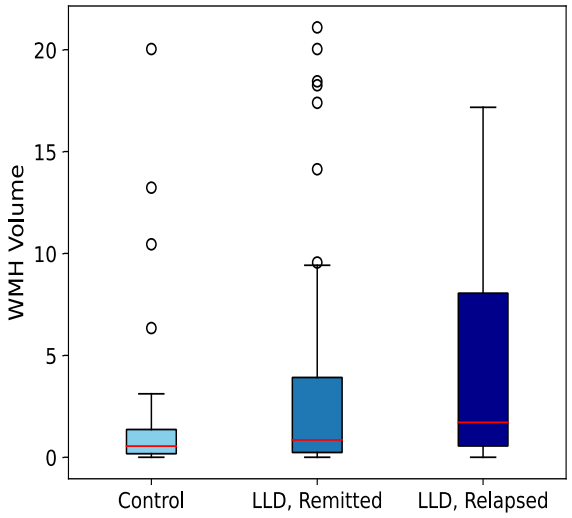
Late-life depression : remission vs. relapse

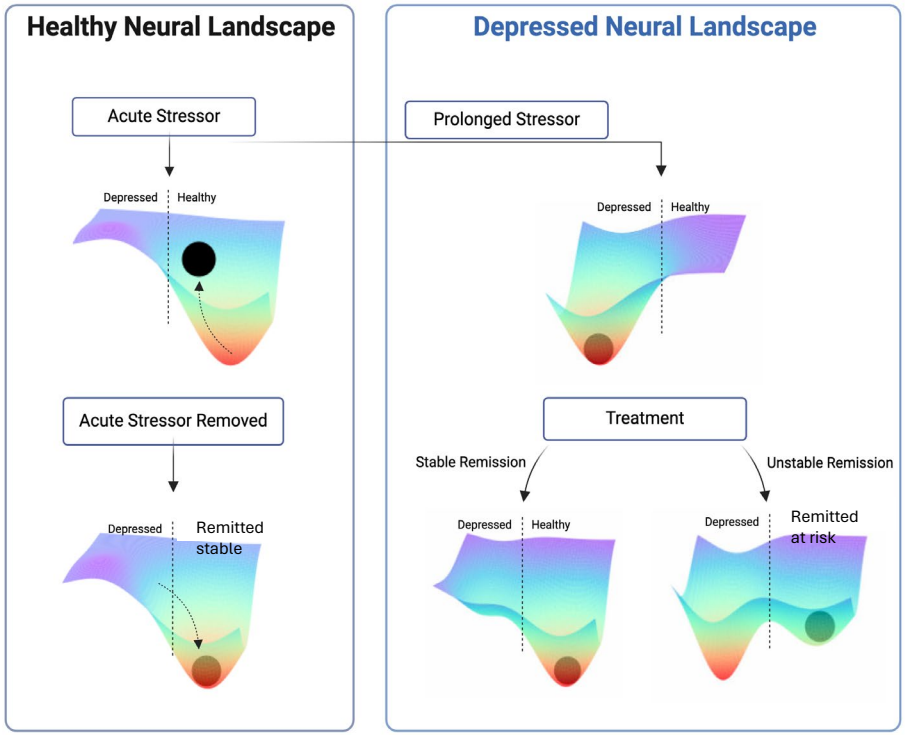
! Relapsers look more like Never depressed

! Remitters acquire a new, stable homeostasis



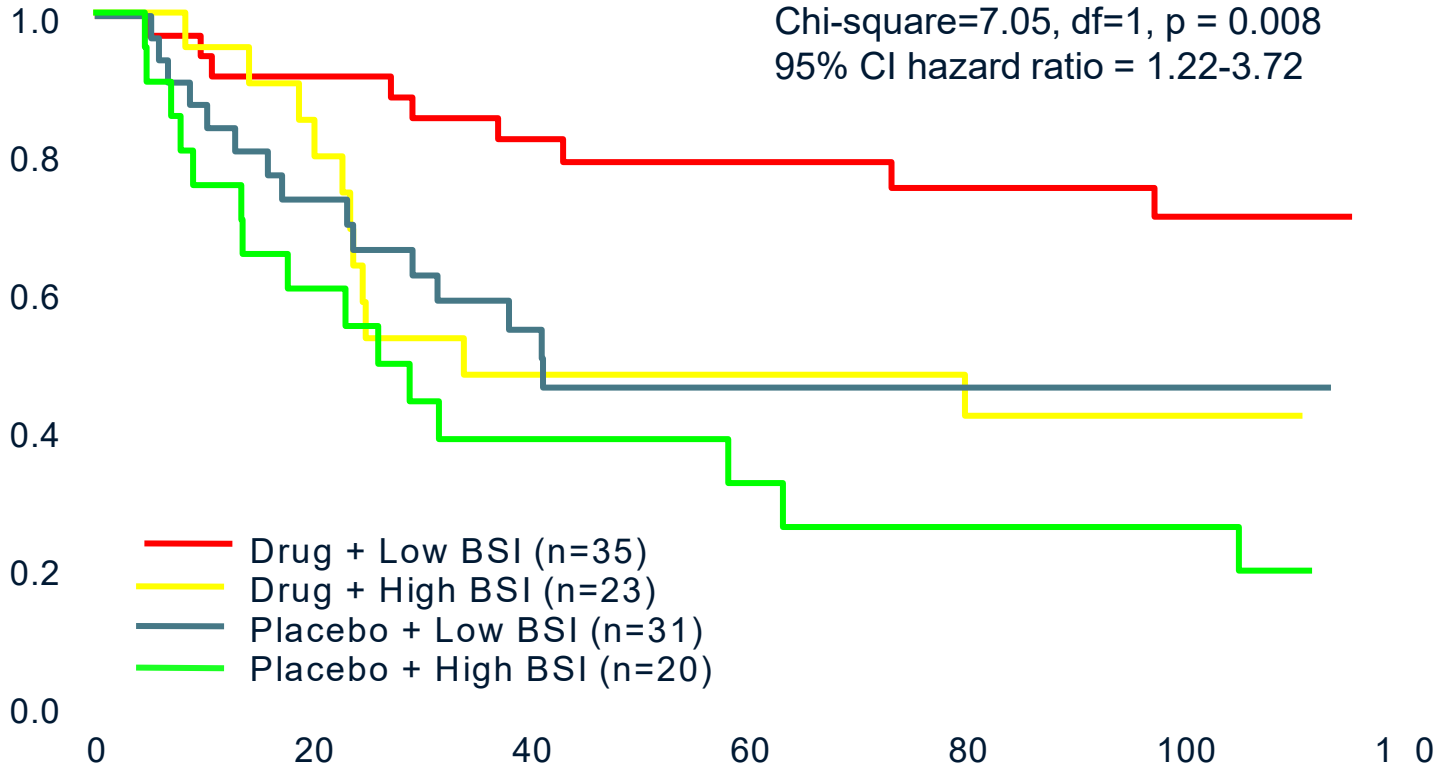
Gerlach et al, in prep



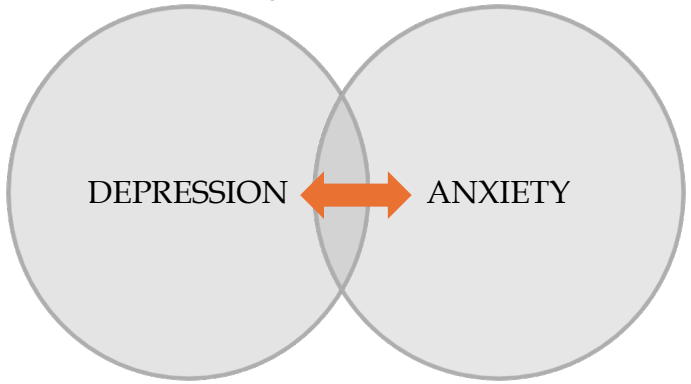


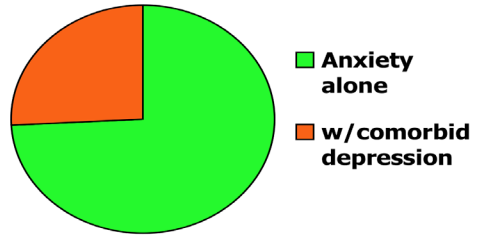
Next step – testing structural networks rigidity

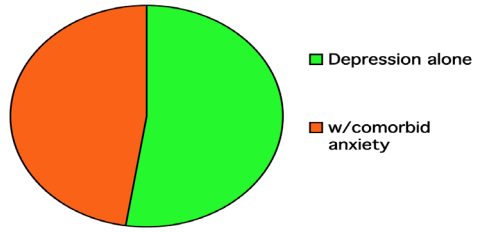
Late-Life Depression and Late-Life Anxiety



Andreescu et al, British J Psych, 2007

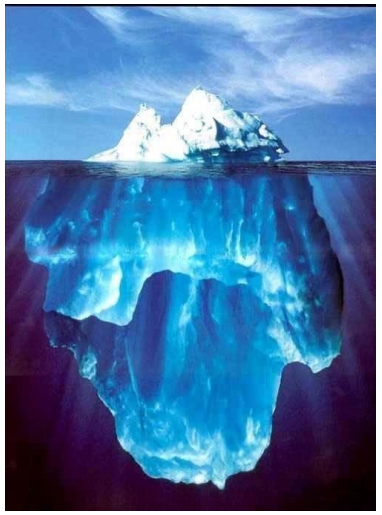






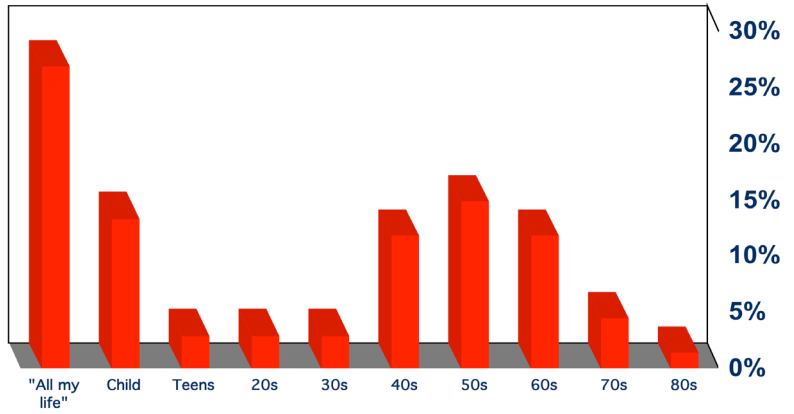
Beekman et al., Am J Psychiatry, 2000

HOW FREQUENT IS ANXIETY LATER IN LIFE?



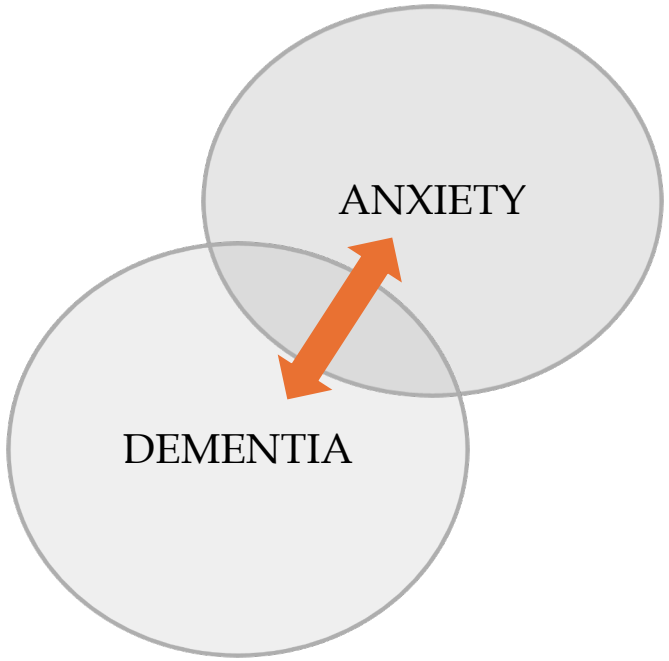
- Older adults and clinicians view anxiety/fear/avoidance as normal in aging
- Most cases hide in the community:
  - 20% of older adults report anxiety symptoms or severe worry
- A categorical diagnosis excludes the majority of cases:
  - Only 20% of older adults with severe worry qualify for a GAD diagnosis
- Women – higher perimenopausal incidence of anxiety/worry

- Older adults tend to:
  - Minimize symptoms
  - Use different language (e.g. “concern” or ”stress” instead of “worry”)
  - Attribute symptoms to physical illnesses



1. Wolitzky-Taylor et al. Depression and Anxiety, 2010
2. Sylke et al. Prevalence of mental disorders in elderly people: The European mentDis_ICF65+ Study, British J Psych, 2017
3. Forlani et al. Anxiety symptoms in 74+ community-dwelling elderly. PLoS One, 2014.
4. Golden et al.: The spectrum of worry in the community-dwelling elderly. Aging Ment Health, 2011
5. Kertz et al. The important of worry across diagnostic presentations. J Anxiety Disord, 2012.
6. Yun Lee et al. Impact of symptomatic menopausal transition on occurrence of depression, anxiety and sleep, Eur Psychiatry, 2023

Anxiety and Dementia – current literature



- 2020 meta-analysis on nine prospective cohorts (N=29,608)[1]:
  - 29% higher risk for all-cause dementia
  - 45% higher risk for AD

- High worry: two-year follow-up indicated >1.5 SD memory decline compared with low worriers [2]
- Anxiety and amyloid/tau burden:
  - Significant association between amyloid/tau and anxiety symptoms severity both in middle aged and older non-demented [3,4]
  - Anxiety moderates the negative effect of amyloid causing a more rapid decline in older individuals without dementia [5]

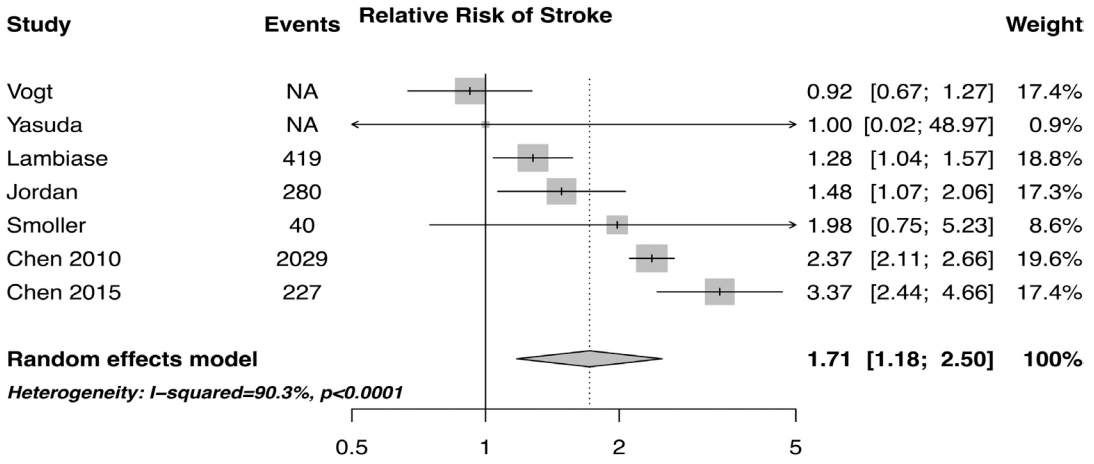
- Cerebrovascular disease:
  - Anxiety participants have 1.65 higher odds of developing vascular dementia [6]

1. Santabarbara et al, J Clin Med, 2020
2. Pietrzak et al, AJGP, 2012
3. Donovan et al, AJP, 2018
4. Lavretsky et al, AJGP 2009
5. Pietrzak et al, BJP, 2014
6. Santabarbara et al, J Clin Med, 2020

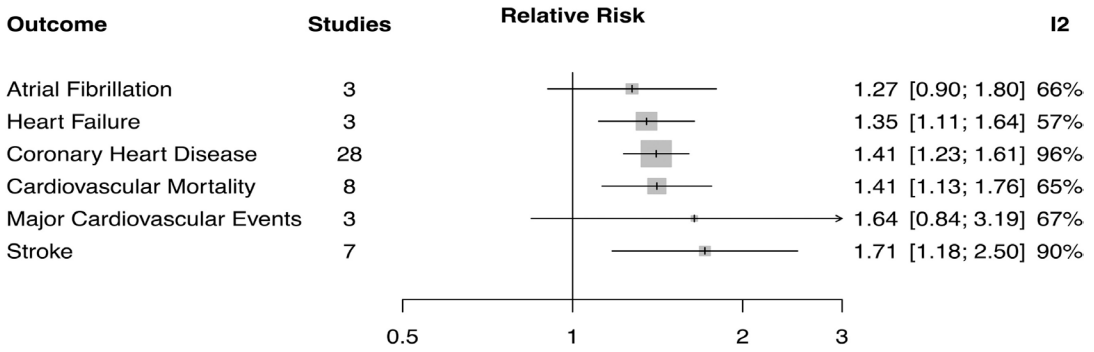
Anxiety and Cerebrovascular Disease

- Anxiety was associated with:
  - 41% higher risk of cardiovascular mortality
  - 41% higher risk of coronary heart disease
  - 71% higher risk of stroke
  - 35% higher risk of heart failure

Association of anxiety with stroke

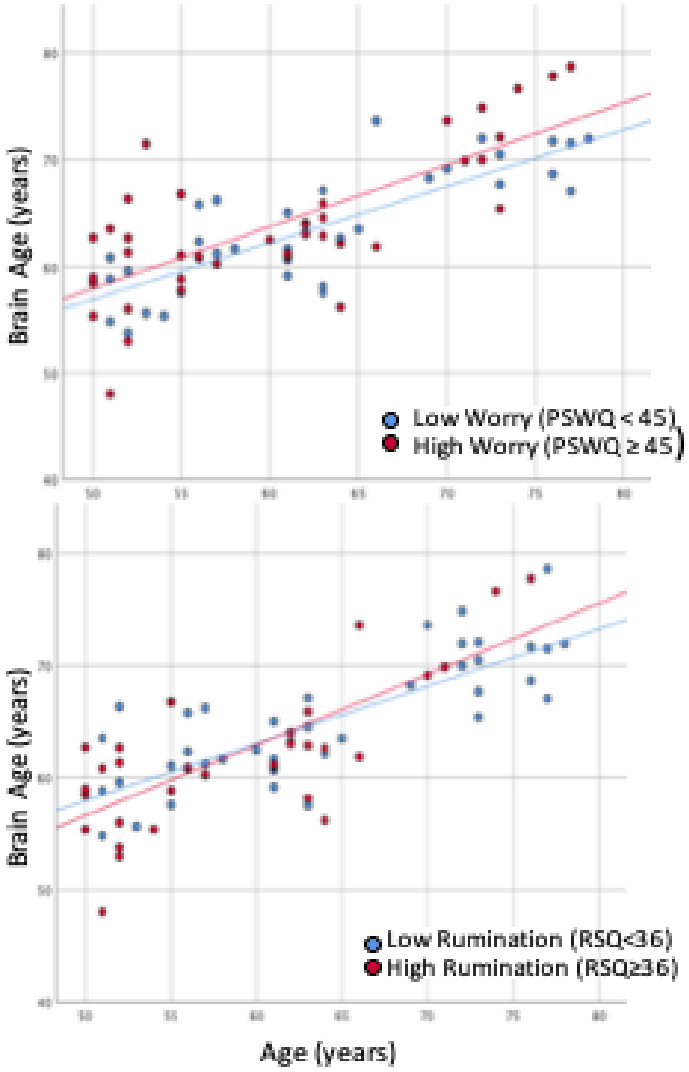


Association of anxiety with cardiovascular disease



Emdin et al., The American Journal of Cardiology, August 2016.

ANXIETY AND DEMENTIA



ELSEVIER

Neurobiology of Aging

Volume 101, May 2021, Pages 13-21

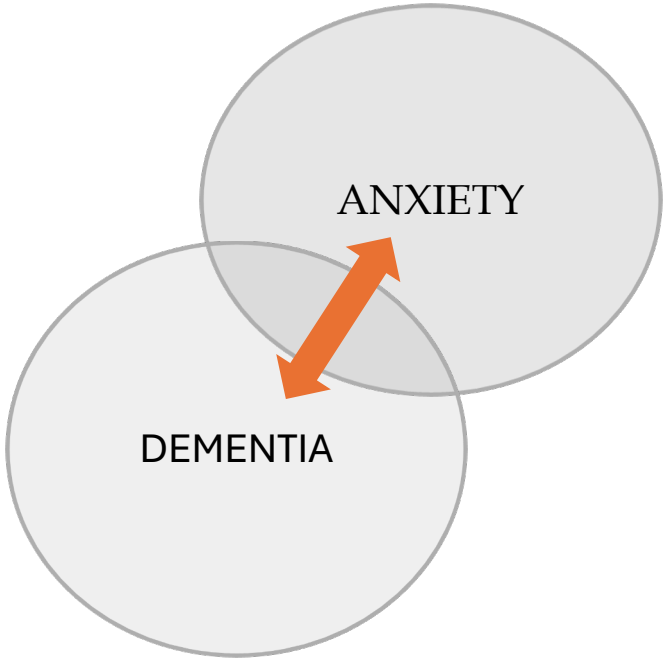
Aging faster: worry and rumination in late life are associated with greater brain age

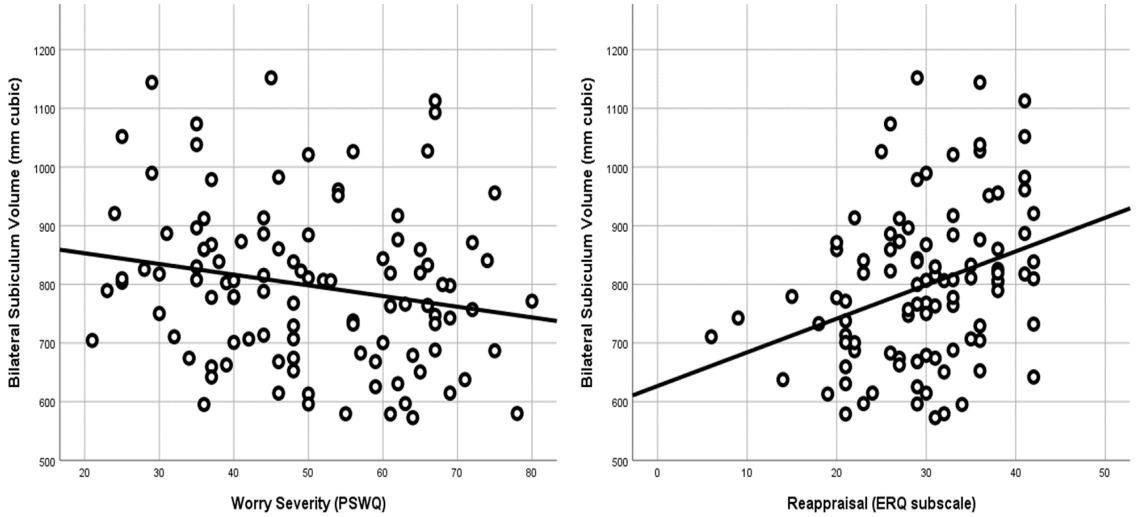
Helmet T. Karim [a], Maria Ly [b], Gary Yu [c], Robert Krafty [d], Dana L. Tudorascu [a, d], Howard J. Aizenstein [a, c], Carmen Andreescu [a]

- N= 78
- ML model to estimate brain age using gray matter density
- Worry and Rumination but not global anxiety are associated with brain aging
- For every point on the PSWQ, brain age was greater by 1.3 months
- For every point on the RSQ, brain age was greater by 1.3 months
- WOMEN'S BRAINS – 4.1 YEARS YOUNGER

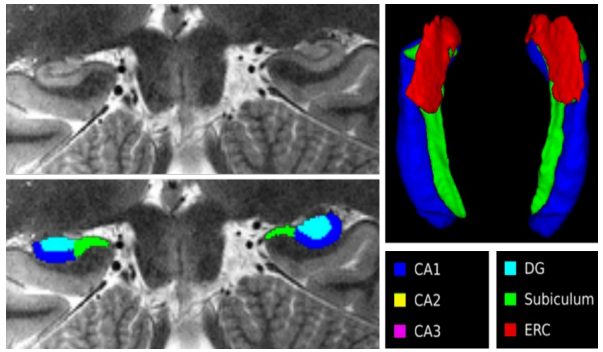
Helmet Karim, PhD

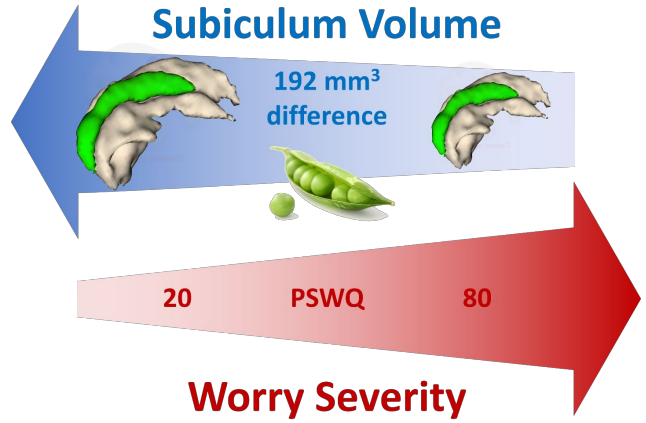
ANXIETY AND DEMENTIA





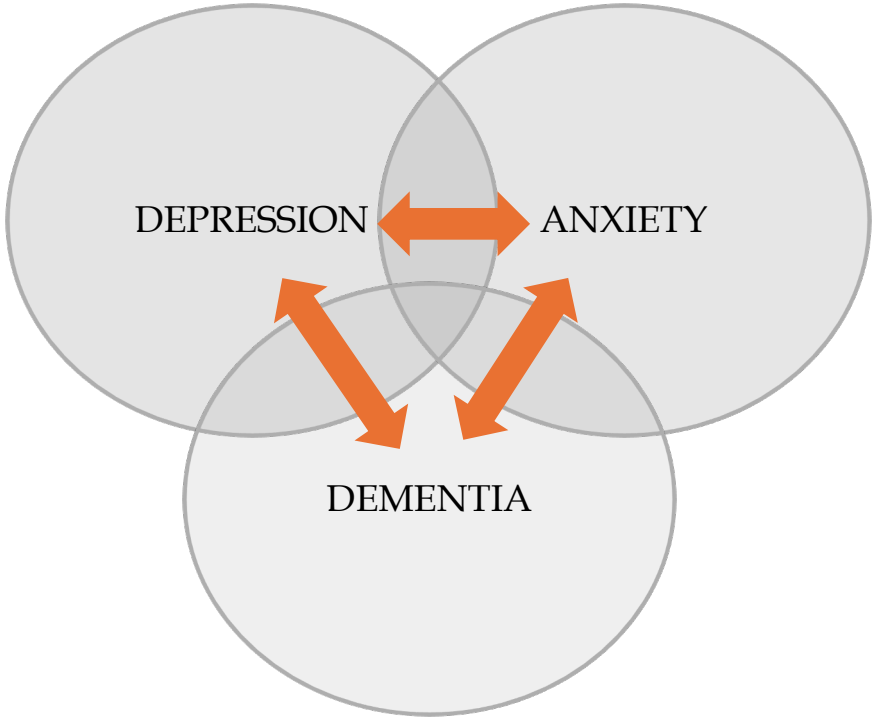
- Hippocampus atrophy
  - N=110
  - Worry severity – lower whole hippocampal volume (r 0.28, p<0.05)
  - Worry severity – lower subiculum volume (r 0.23, p<0.05)
  - Greater use of reappraisal – larger subiculum and CA1 volume
  - Rumination and anxiety severity – non sig



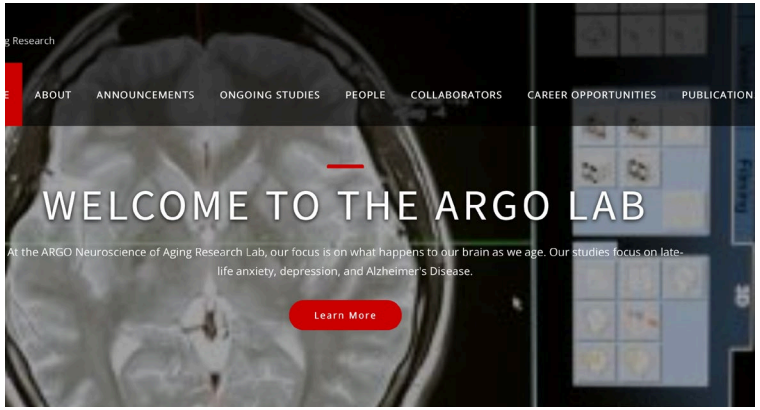


Karim et al, Neurobiology of Aging 2024 (in press)

THE DARK TRIAD - CONCLUSIONS



- Depression and Anxiety Independently increase Dementia risk through multiple pathways
- Perimenopause is an inflection point for mood and anxiety symptoms in older women
- Markers of treatment response differ in women and men
- The brain ages differently in women and men
- Old age – Chickens are coming home to roost



- https://argo.pitt.edu

Thank you!

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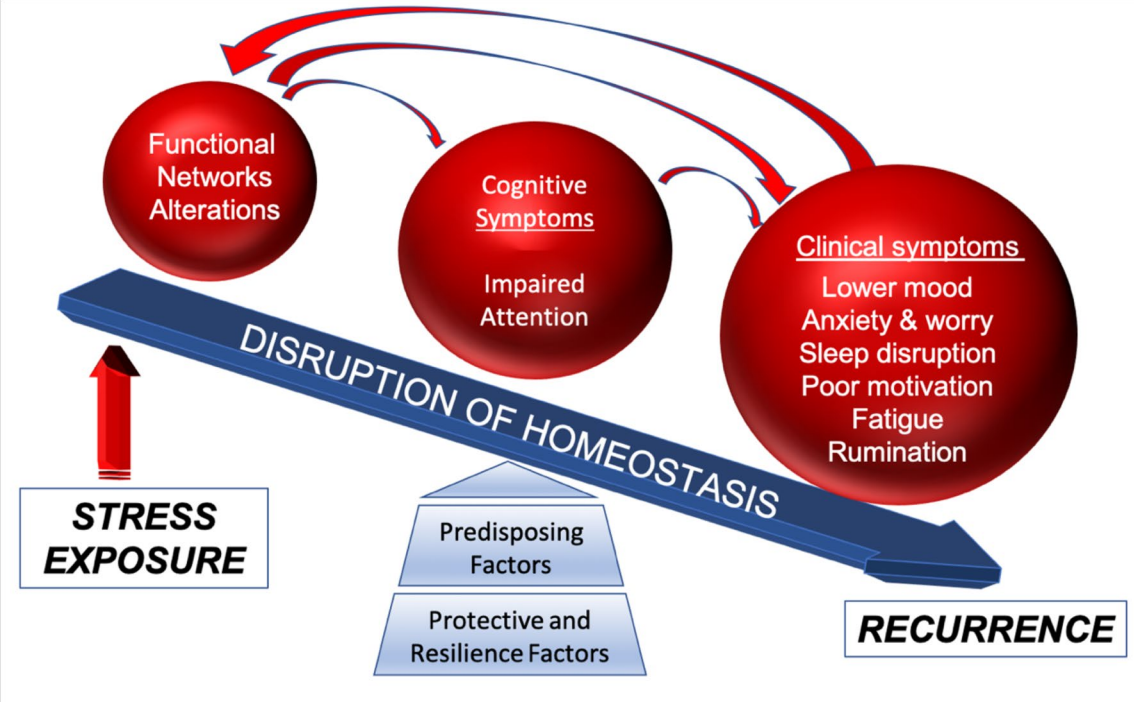
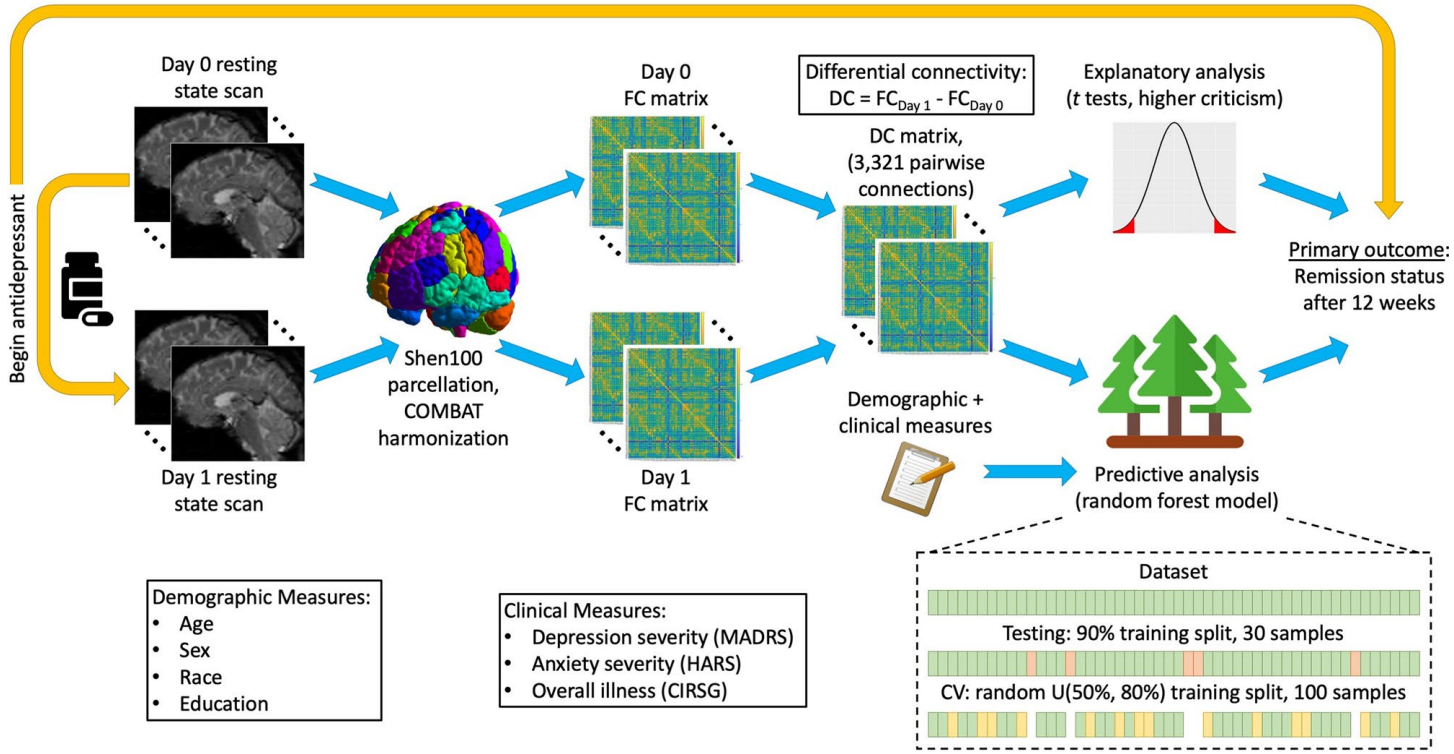
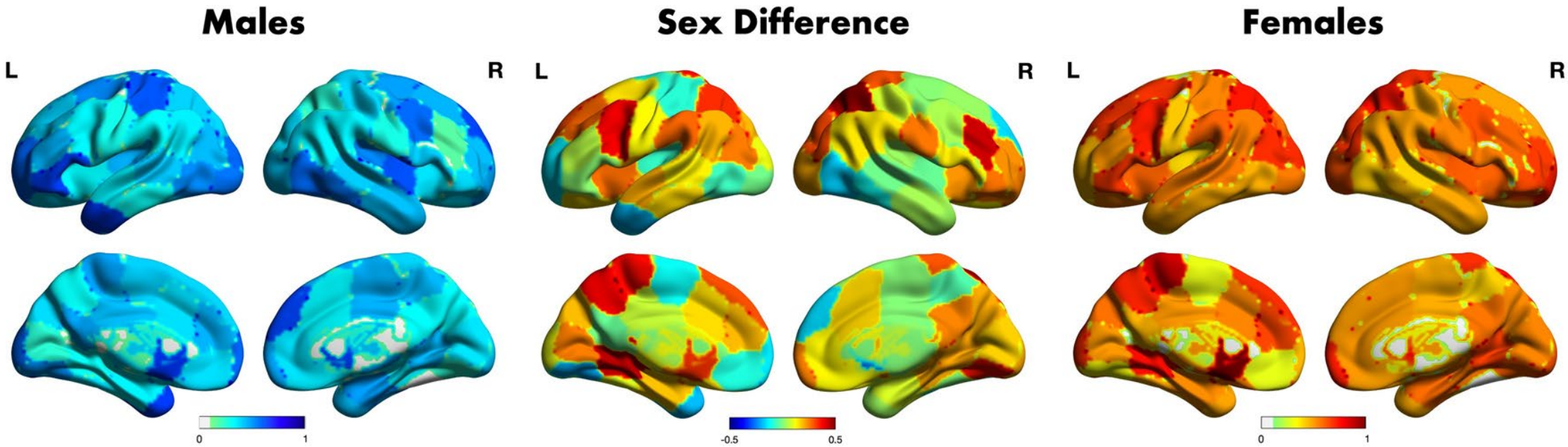


Functional Networks in Late-Life Depression – Sex matters



Gerlach et al, Molecular Psychiatry 2023, Jul 6:10

Differential connectivity importance for prediction of remission



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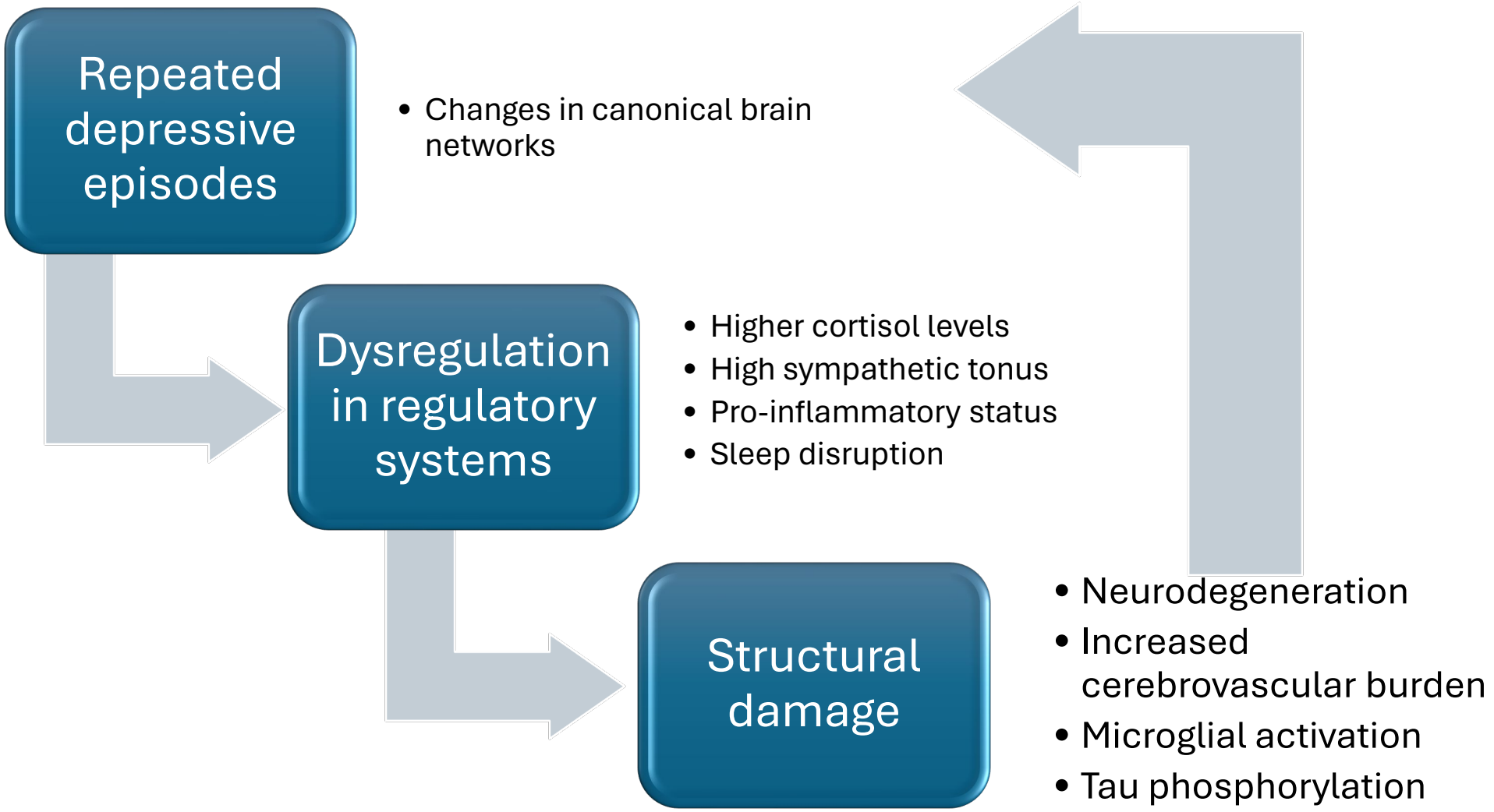


Anxiety disorders and Vascular Disease

Impact of panic, phobia and worry on a 3-yr onset of CVD

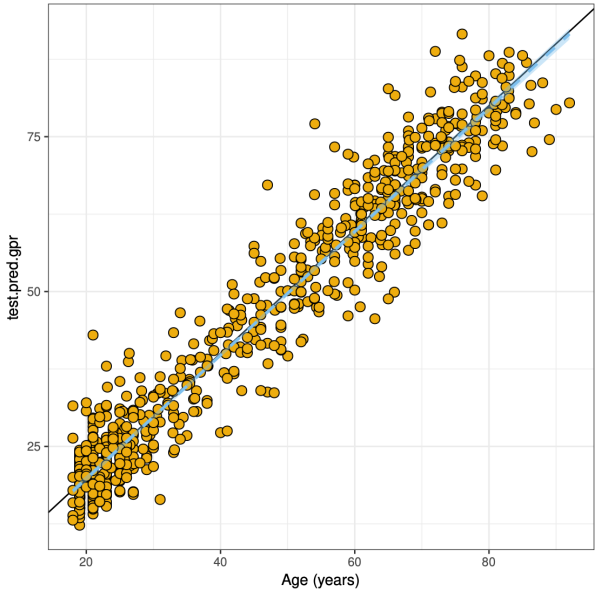
	Adjusting for socio-demographics [a]		Adjusted for behavioral variables[b]		Adjusted for comorbid somatic conditions and comorbid psychiatric disorders[c]		Adjusted for significant covariates from previous models[d]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Any anxiety disorder[e]	1.41	0.59–3.39	1.24	0.53–2.91	1.30	0.60–2.84	1.29	0.52–3.19
Panic (panic disorder and panic attacks)	1.20	0.44–3.24	1.10	0.42–2.85	1.03	0.45–2.37	1.09	0.39–3.06
Phobia (social phobia and agoraphobia)	0.64	0.16–2.48	0.55	0.14–2.09	0.50	0.13–1.98	0.60	0.15–2.42
Worry (generalized anxiety disorder)	3.82	1.48–9.90	3.26	1.16–9.17	4.62	1.94–10.99	3.39	1.30–8.84

Multivariate model of the impact of worry on 3-yr onset of CVD in the general population

Variable	OR	95% CI
Worry (generalized anxiety disorder)	3.39	1.30–8.84
Socio-demographics		
Male gender	2.00	1.07–3.72
Age (per SD)	1.61	0.93–2.81
Education	0.82	0.59–1.14
Living without partner	2.22	1.27–3.91
Behavioral variables		
Smoking	2.25	1.06–4.75
BMI (per SD)	1.19	0.92–1.53
Comorbid somatic conditions		
Diabetes mellitus	3.20	1.16–8.79

Batelaan et al, J of Anxiety Disorders, 2014

Amyloid Negative BrainAge (ANBA) model



Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Improving brain age prediction models: incorporation of amyloid status in Alzheimer's disease

Maria Ly[a,b], Gary Z. Yu[c], Helmet T. Karim[a], Nishita R. Muppidi[c], Akiko Mizuno[a], William E. Klunk[a], Howard J. Aizenstein[a,c,*], for the Alzheimer's Disease Neuroimaging Initiative[1]

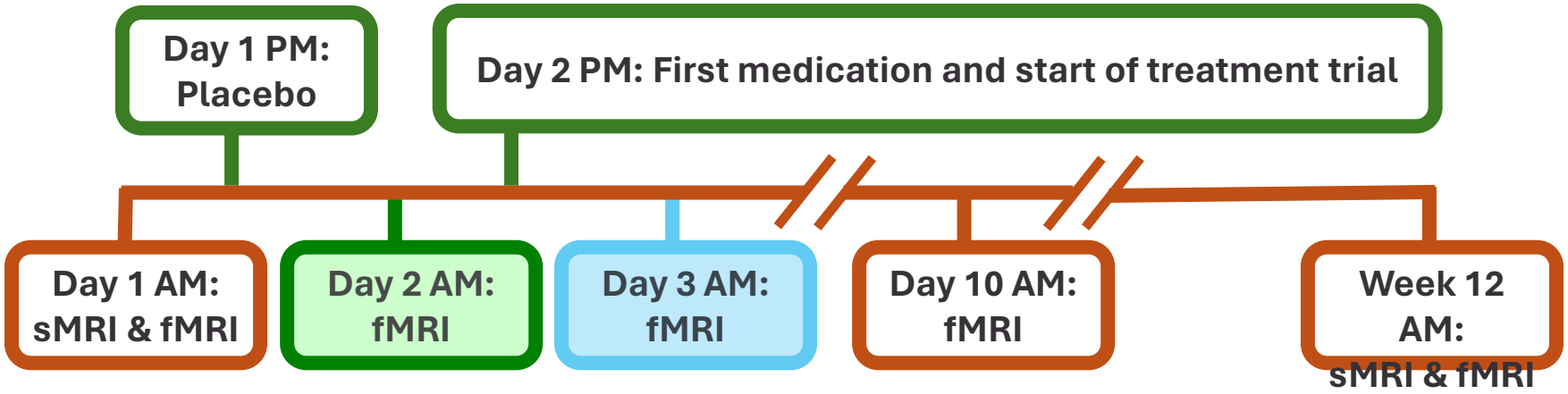
[a] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
[b] Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA
[c] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA

- Model trained on N = 1256 with and without amyloid pathology
- Age range 20-85
- Incorporated amyloid pathology information into model
- Was able to delineate significant differences in brain age relative to chronological age between cognitively normal individuals with and without amyloid
- Improved prediction of chronological age over the brainageR model

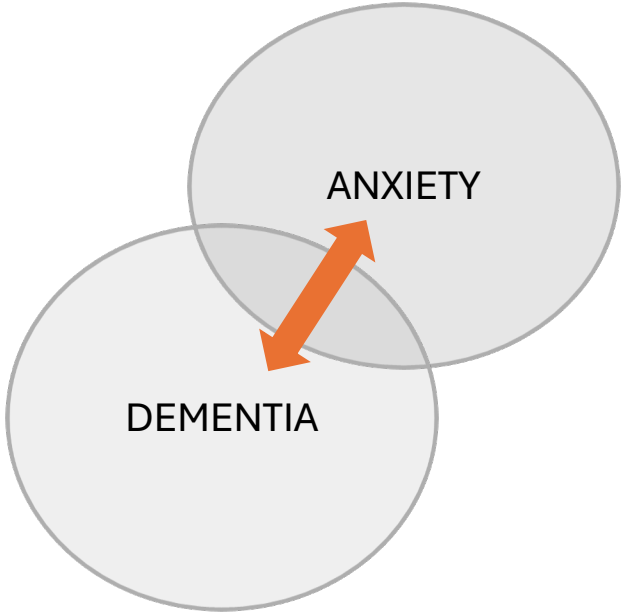
- Generates predicted brain-age from T1-weighted MRI's
- Gaussian Processes Regression with Principal Components Analysis
- Model trained on N = 3377
  - 7 public datasets from US, UK, Australia, China
  - Age mean = 40.6 years, range 18-92 years)
- Model tested on several independent cohorts

Helmet Karim, PhD

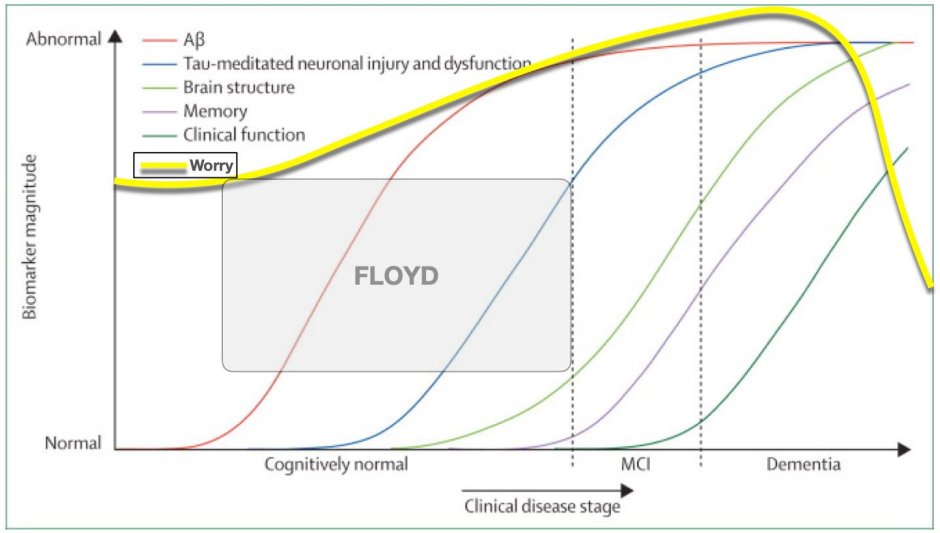
Study Design



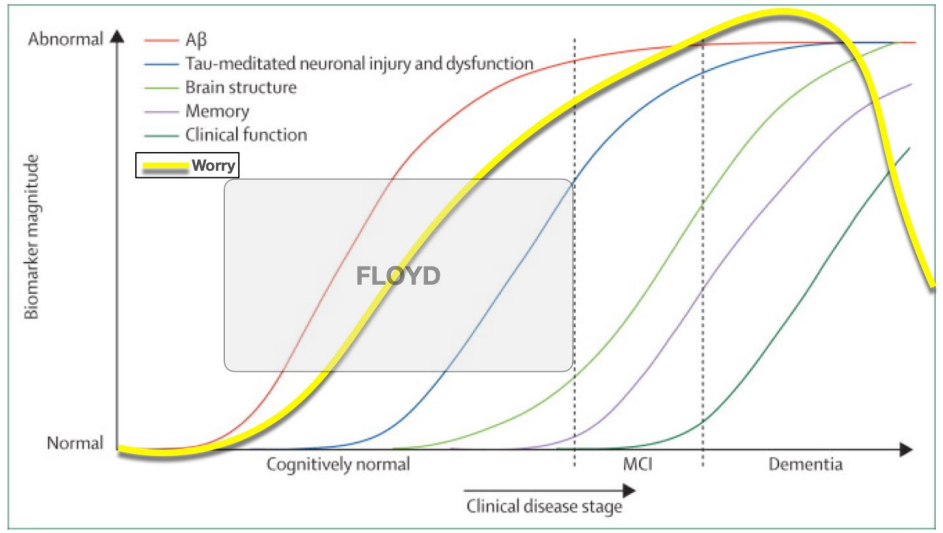
- Inclusion: At least 55 years old, DSM IV criteria for MDD, Montgomery-Asberg depression rating scale (MADRS) > 15.
- Exclusion: History of other disorders with known effects on mood.
- Drug: Venlafaxine – serotonin-norepinephrine reuptake inhibitor
- Returned weekly/bi-weekly to have dosage adjusted (175 mg maximum)
- Non-responders (at half way) had their dose increased (350 mg maximum).
- Remission (or those that improved during the study) was defined as MADRS < 10 for at least 2 consecutive weeks



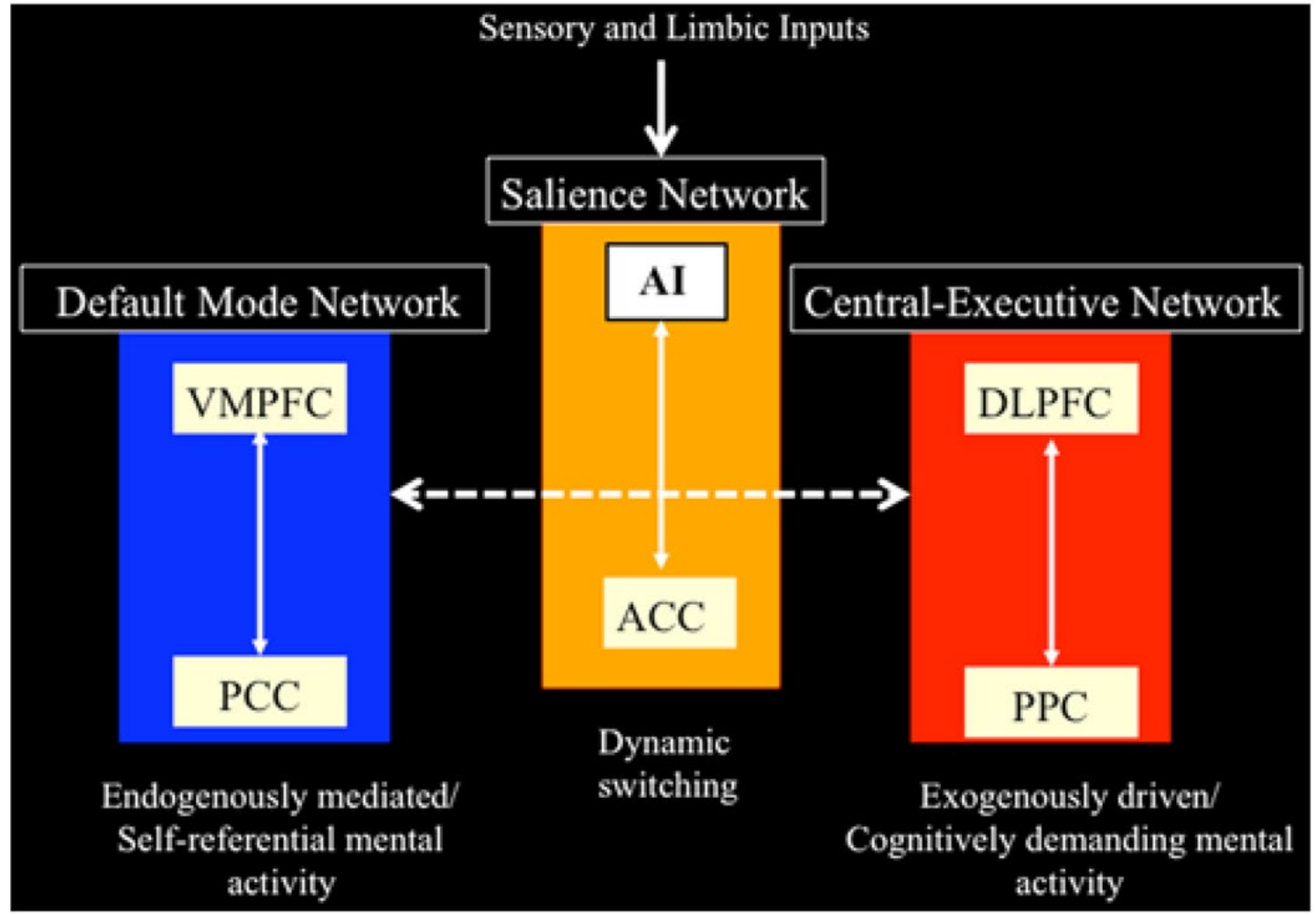
Anxiety and Dementia



Worry as risk factor



Worry as prodrome


Sensory and Limbic Inputs
Salience Network
AI
Default Mode Network
Central-Executive Network
VMPFC
DLPFC
ACC
PCC
PPC
Dynamic switching
Endogenously mediated/ Self-referential mental activity
Exogenously driven/ Cognitively demanding mental activity