

Mass General Brigham

The Landscape of Cognitive and Emotional Functioning in Depression and the Aging Brain


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Disclosures

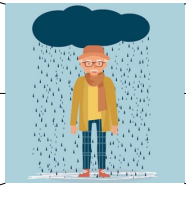
- QB Tech® ADHD Expert Advisory Panel Member



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Late Life Depression



~6% meet DSM criteria for Major Depressive Disorder; 15% when include milder symptom severity


Worsens medical outcomes, increases disability, hastens cognitive decline, increases risk for dementia

Symptom presentation frequently not typical of that observed in younger adults.

1/2 to 2/3 fail to respond to remit with first-line SSRI or SNRI.

High rate of medical comorbidities, resulting in under-diagnosis and under-treatment.

Little evidence from RCTs to guide alternative treatment options.

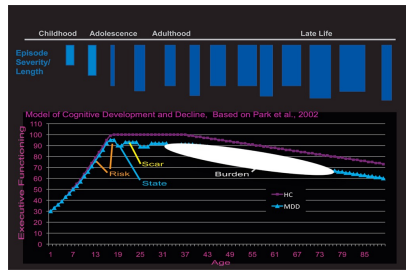


Crisancho et al., (2019). Optimizing outcomes of treatment resistant depression in older adults. *Am J Geriatr Psych*, 27(10), 1138-52; Gorfine (2001). Late-life depression. *Eur Arch Psychiatry Clin Neurosci*, 251, Suppl 2: 1157-62; Almeida & Smy (2013). Epidemiology of late-life mood disorders. In *Late-Life Mood Disorders*, Oxford University Press, New York, NY.

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Lifetime Trajectory of LLD

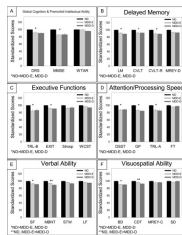


Langenecker & Weisenbach, Unpublished

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Neurocognitive Functioning during Active and Remitted Depression among 438 Older Adults



- Most pronounced differences in attention/processing speed, but all domains impacted
- Remission of depression does not predict improvement in cognition



Koenig et al. (2015). Neuropsychological functioning in the acute and remitted states of late-life depression. *J Alzheimer's Dis*, 45(3), 175-185.

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Neurobiological Signature of the LLD Syndrome

- Gray matter atrophy in regions relevant for cognitive functioning, including hippocampus and prefrontal cortex (e.g., Lebedeva et al., 2015; Vu & Alzstein, 2013).
- Increased white matter hyperintensities and changes in white matter microstructure (e.g., Park et al., 2015; Taylor et al., 2013).
- Differences in functional connectivity during the resting state and in activation during task challenge (e.g., Ajilore et al., 2014; Alexopoulos et al., 2012; Eyre et al., 2016; Rao et al., 2016; Weisenbach et al., 2014)
- Higher neuroinflammation (Su et al., 2016), reduced 5-HT (1A) in dorsal raphe nucleus (Weltzer et al., 2004) revealed by PET



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Cognitive Control Network Functioning in Late Life Depression (LLD)

Executive dysfunction in LLD associated with

- Illness chronicity
- Disability
- Poor or delayed response to antidepressant treatment
- Increased risk of suicide



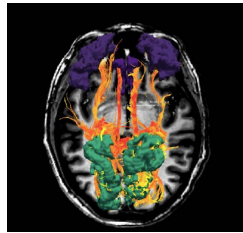
Alexopoulos et al., 2000; Kiosses et al., 2001; Manning et al., 2015; Richard-Devantoy et al., 2012

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Cognitive Control Network (CNN)

- Frontoparietal circuit that comprises the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, and posterior parietal cortex
- Relevant to top-down tasks requiring attention, such as attentional switching, decision-making, and working memory



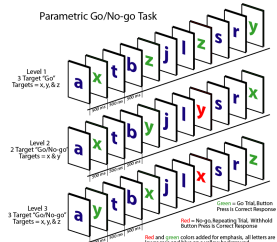
Todaro-Venardis & Allaire (2014). Brain network dysfunction in late-life depression: A literature review. *J Geriatric Psychiatry Neurol*, p. 7.

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Cognitive Control Probe

Parametric Go/No-go Task



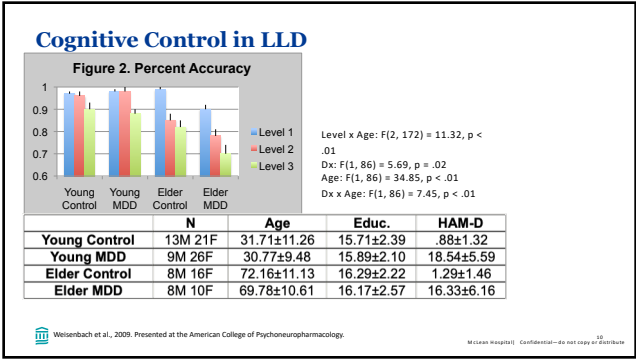
This task measures how well someone sustains attention and can inhibit responses to non-relevant stimuli.



Adapted from Langenecker SA, & Nielson, KA (2003). Frontal recruitment during response inhibition in older adults replicated with fMRI. *Neuroimage*, 20(2), 1384-1392.

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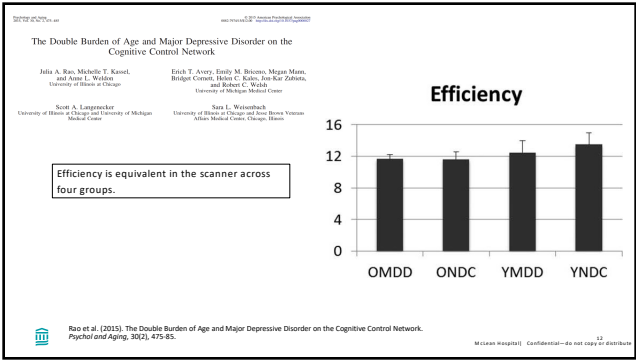
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Cognitive Control and its Neural Substrates in LLD

Variable	OMDD (n = 24)	ONDC (n = 23)	YMDD (n = 16)	YNDC (n = 18)
Age- mean years (SD)	66.8(8.2)	67.9(8.1)	26.4(4.4)	21.5(2.6)
Education- mean years (SD)	15.9(2.7)	16.7(2.1)	16.7(2.1)	15.0(1.8)
Sex- % female	58	44	38	50
Hamilton Depression Rating Scale- mean(SD)	15.7(5.2)	0.9(1.0)	15.8(3.8)	0.8(1.2)
Years of illness (MDD only)- mean years (SD)	39.8(16.8)	NA	9.7(5.9)	NA
Psychotropic Medication- %	78	NA	32	NA

Rao et al. (2015). The Double Burden of Age and Major Depressive Disorder on the Cognitive Control Network. *Psychol and Aging*, 30(2), 475-85. Meaningful Confidential—do not copy or distribute

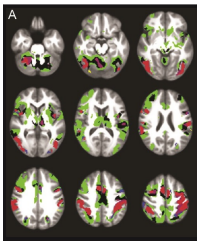
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Cognitive Control and its Neural Substrates in LLD

ACTIVATION DURING CORRECT TARGET HITS ON PGNG-LEVEL 1. Areas of convergence in Go networks across all four groups (red), at least three groups (YMDD, ONDC, OMDD in purple), only in the older groups (black), only in the MDD groups (blue), and only in the older MDD group (green).

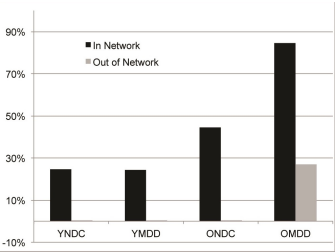


Rao et al. (2013). The Double Burden of Age and Major Depressive Disorder on the Cognitive Control Network. *Psychol and Aging*, 30(2), 475-85.

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Cognitive Control and its Neural Substrates in LLD

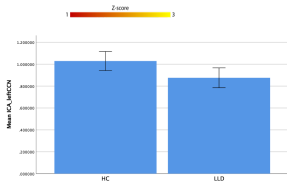


Rao et al. (2013). The Double Burden of Age and Major Depressive Disorder on the Cognitive Control Network. *Psychol and Aging*, 30(2), 475-85.

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Resting State Network Strength-Left CCN



Variable	MDD (n = 18)	HC (n = 31)
Age* M(SD)	66(2)	70(6)
Education- M(SD)	16.2(2.5)	16.8(2.4)
Sex- % female	31	42
HAM-D* M(SD)	18.5(10.0)	6.7(7.8)
HAM-A* M(SD)	8.0(1.9)	1.8(2.5)


Weisenbach et al. (in Progress).

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Left CCN Strength at Rest Predicts Executive Functioning

Outcome Measure	Model 2 Adj. R2	DMN Adjusted B	DMN p
D-KEFS Category	.13	.51	<.01
Animal Naming	.00	.32	.04
Phonemic Fluency	.12	.38	.03

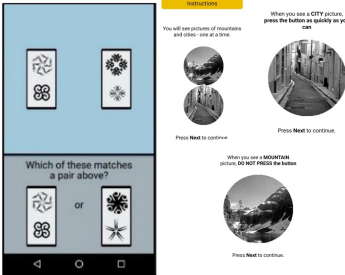
 Weisenbach et al. (In Progress).

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Brief-Burst Mobile Cognitive Assessment

- Allows for measurement of day-to-day cognitive functioning in real-world settings, thus allowing for:
 - Measurement of variability across time



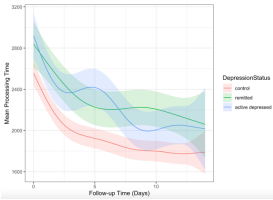
 Adapted from Shuangyi Li, Scott M. Marder, MD, & Shuangyi Li (2022). Daily or Cognitive tests among older adults.

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Brief-Burst Mobile Cognitive Assessment: Processing Speed

- After covarying for age, sex, and education:
 - processing speed at noon and in the afternoon (4 pm) tends to be faster than in the morning
 - actively depressed and remitted patients tend to have lower response speed than controls



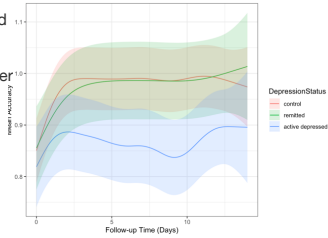
 Patrick et al. (In Progress).

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Brief-Burst Mobile Cognitive Assessment: Cognitive Control

- After covarying for age, sex, and education:
- increasing trend of accuracy over time
- actively depressed are less accurate than other groups.



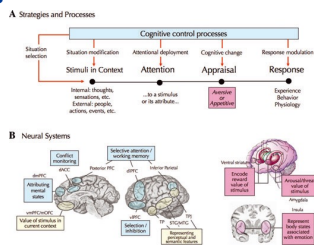
Parikh et al. (in Progress)



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Role of Cognitive Control in Emotion Processing

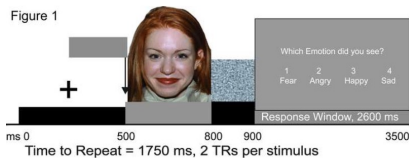


Ochsner KN, Silvers JA, & Buhle (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annu. Rev. Acad. Sci.*, 1251, E1-E24.

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Emotion Processing Probe

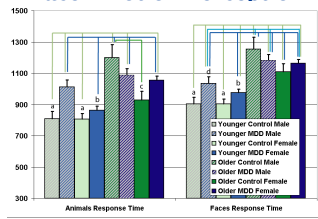


Langecker SA, Cavenny AF, Giondini B, Young EA, Nelson KA, Rapoport LJ, Bielewicz LA, Mordhorst MJ, Marcus S, Yodanis CL, Kessler R, Bennett S, Dubowitz JR. *Psychiatry Res.* 2007 Aug; 151(2-3):143-154.

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Sex and Age Interactions with Depression Status on Face Emotion Perception

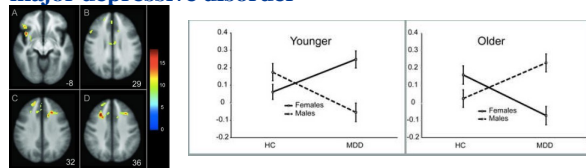


Wright SL, Langenecker SA (2009). Differential risk for emotion processing difficulties by gender and age in Major Depressive Disorder. In Hernandez & Alonso S (Eds.), Women and Depression. New York: Nova Publishers.

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Age and sex modulate the neural circuitry supporting facial emotion processing in adults with major depressive disorder



Birbafla BM, Ragupathi LI, Kasari MT, Bellaroukas LA, Zubieta JC, Weisenbach SL, Langenecker SA, Am J Geriatr Psychiatry. 2015 Mar;23(3):304-13

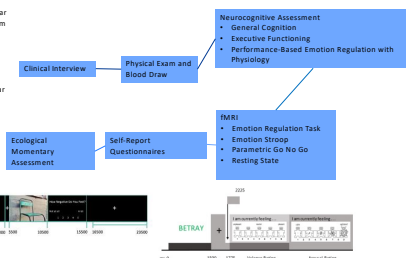
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Developing Informed Treatment Targets

204 adults aged 55-79, stratified by age group (5-year epochs), depression symptom severity, and sex

Additional n = 60 with amnesic MCI (Supplement)
Additional n = 20 with Bipolar Disorder (Patrick)



RO1 MH 116033

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Treatment

Problem Adaptation Therapy (PATH; Kiesses et al., 2015)

12-week RCT of PATH versus supportive therapy (ST) among 74 older adults with depression, cognitive impairment, and disability
PATH combines problem-solving approaches with compensatory strategies, environmental adaptations, and caregiver participation
PATH had reduced depression symptom severity and disability and greater remission than ST

ENGAGE (Alexopoulos et al., 2016)

9-weekly sessions in open-label trial of 48 nondemented older adults with MDD
ENGAGE uses reward exposure to promote behavioral activation
Change in behavioral activation predicted improvement in depression signs and symptoms



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Summary and Conclusion

- Late life depression is a complex disease that has historically been difficult for care providers to effectively manage, with few RCTs to guide treatment decisions
- Depression in late life impacts cognitive control and emotion processing, at the levels of brain and behavior, and likely play a role in disease chronicity and relapse
- There are a number of emerging treatments that are more specialized in treating depression during late life



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Faculty Collaborators

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