Effects of Non-Pharmacological Treatments on Cognition in Depression

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Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression

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Disclosures

Consulting/honoraria (past 3 years)

- Advanced Neuro Technology North America Inc.
- Otsuka America Pharmaceutical, Inc.
- Pfizer
- Servier

Grants

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- NARSAD Independent Investigator Award
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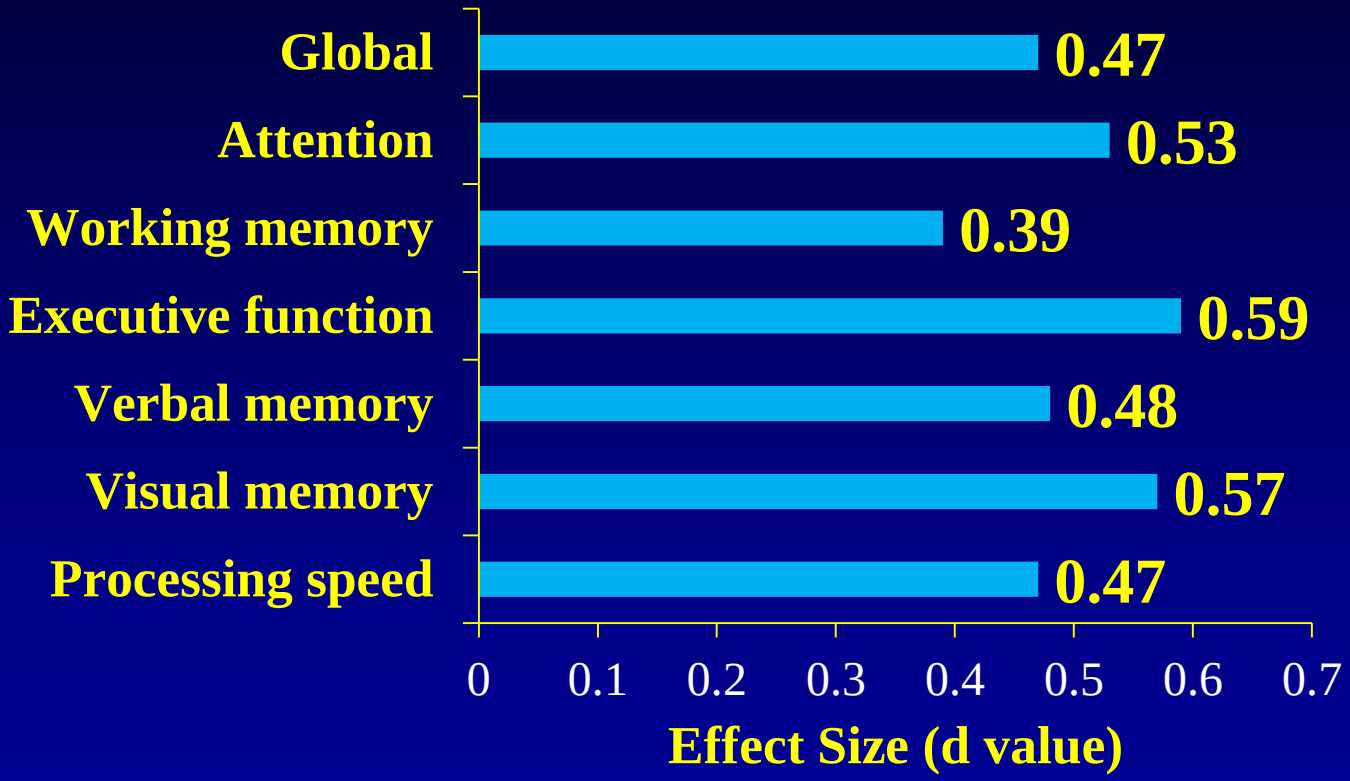
- RWJ Health and Society Scholars Grant

Cognitive Deficits in Depression

- Cognitive deficits in several domains: executive function, attention, memory, psychomotor speed
- Negative effects on: social and occupational outcome (Withall et al., 2009), functional recovery (Jaeger et al., 2006), employment status (Baune et al., 2010), daily activities (Kiosses and Alexopoulus, 2005), compliance with AD treatment (Martinez-Aran et al., 2009), suicide risk (Westheide et al., 2008), relapse risk (Alexopoulus et al., 2000)
- Cognitive deficits are present during first MDE (ES: 0.30-0.50) (Lee et al., 2012)

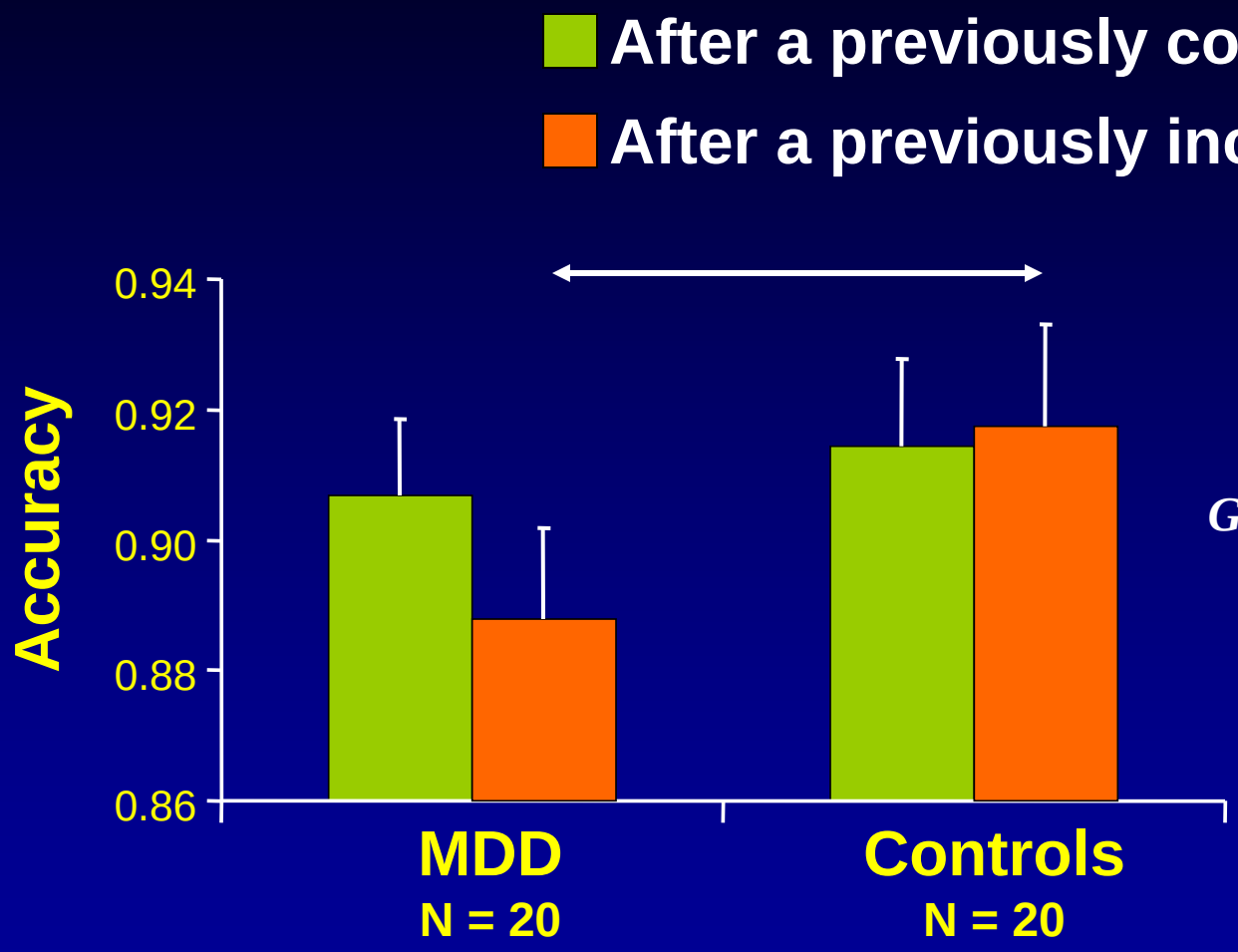
McIntyre et al., 2013; Rock et al., 2014; Trivedi and Greer, 2014

- **Cognitive Deficits in Depression (cont.)**
  - **Bora et al. (2013): meta-analyses (27 studies, 895 MDD vs. 993 HC) in remitted (euthymic) individuals**



  - **Effects not modulated by # MDE, duration of illness, current (residual) symptoms**

- **"Catastrophic" reactions to errors in depression**

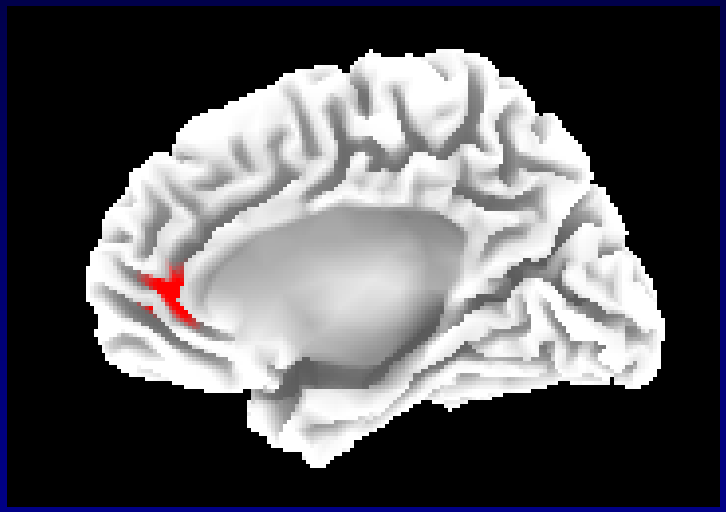


Group x *Condition*
F(1,38) = 6.78
p < .015

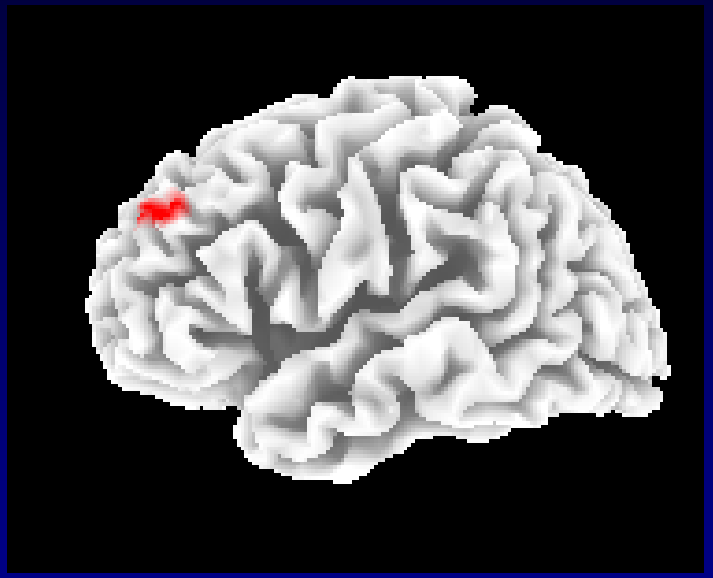
Stroop task
Green *vs.* Green

MDD: Holmes & Pizzagalli, 2008
Subclinical depression: Pizzagalli et al., 2006
At-risk subjects: Holmes et al., 2010

- **ERP correlates of abnormal error processing in MDD**



80 ms post-error:
Dysfunctional rostral ACC activation



472 ms post-error:
Disrupted functional coupling between rostral ACC and Prefrontal Cortex

Holmes and Pizzagalli, *Archives of General Psychiatry*, 2008

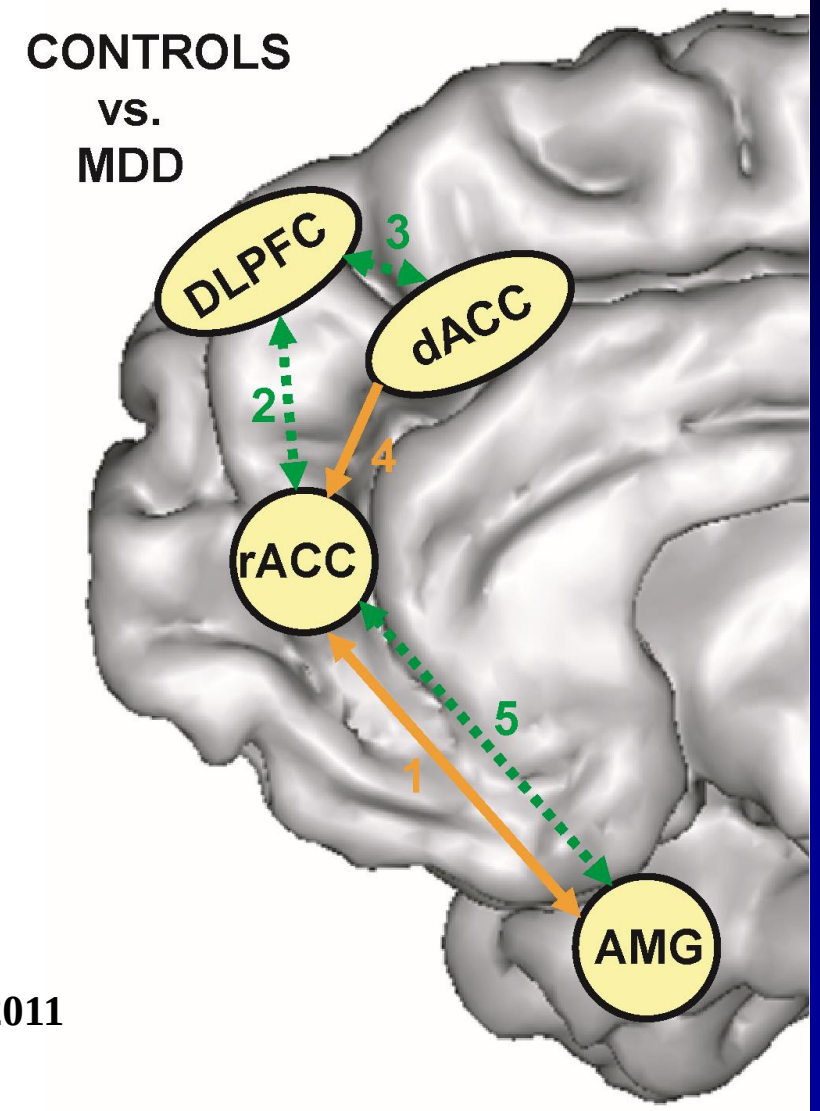
• Frontocingulate Dysfunctions in MDD

Negative cues or negative self-referential processing (in MDD):

- ↓ functional coupling between rACC/DLPFC (arrow 2) and dACC/DLPFC (arrow 3)

- ↑ functional coupling between the rACC and the amygdala (arrow 1)

→Failures to deactivate the rACC and amygdala during affective and cognitive challenges → Rumination & cognitive deficits?



Pizzagalli, *Neuropsychopharmacology Review*, 2011

Kaiser et al., *JAMA Psychiatry*, in press

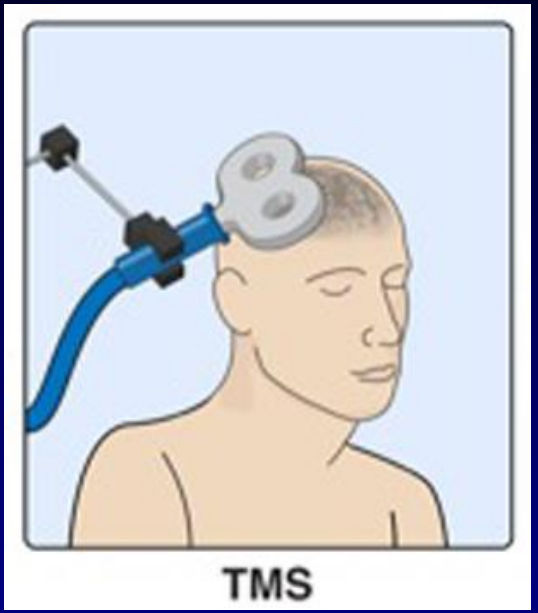
- **Non-Pharmacological Treatments for Cognition**

1. **Transcranial Magnetic Stimulation (TMS)**
2. **Transcranial Direct Current Stimulation (tDCS)**
3. **Psychotherapies**
4. **Cognitive Remediation (see Dr. Bowie's talk)**

- **Transcranial Magnetic Stimulation (TMS)**

A. What is it?

- Application of electromagnetic pulses through a coil
- Typically administered over the left DLPFC



B. Assumed action?

- Restore GABAergic interneuron dysfunction?
- Pulses trigger action potentials; effects are frequency-dependent:
  - High-frequency (e.g., 20 Hz): ↑ cortical excitability
  - Low-frequency (e.g., 2 Hz): ↓ cortical excitability

Edwards & Alvaro Pascual-Leone, 2014 Mondino et al., 2014

- **Transcranial Magnetic Stimulation (TMS)**

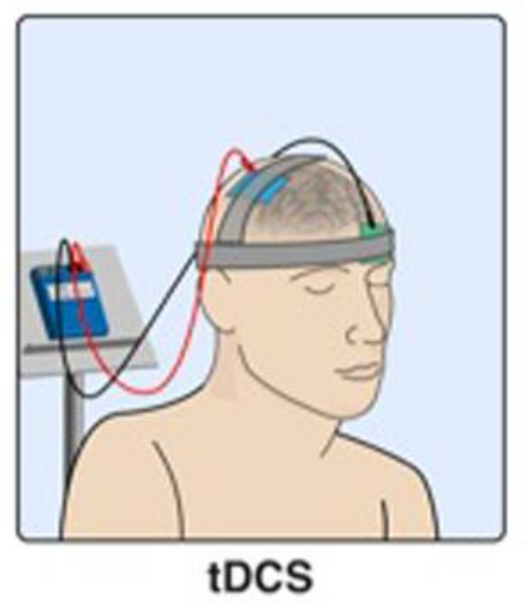
C. Effects on cognition (Tortella et al., 2014):

- 11 blinded, randomized, sham-controlled studies (all targeting left BA9/46): [5-29 sessions, 1-4 weeks]
  - 3 of 11 showed beneficial effects on executive function
  - 8 of 11: No beneficial effects
  - Other sporadic improvements: Long-term memory, verbal memory encoding, attention, motor speed
- Demirtas-Tatlidede et al. (2014):
  - 8 of 13 shamed controlled trials: no differences between active and sham rTMS on cognition
  - Most of open studies (n =11): effects on cognition!

Demirtas-Tatlidede et al., 2014 ; Mondino et al., 2014 ; Tortella et al., 2014

- **Transcranial Direct Current Stimulation (tDCS)**

A. What is it?



- Application of low-intensity direct current (0.5-2 mA) over the scalp between two electrodes (Nitsche et al., 2003)
- Current delivered by a battery-driven constant current stimulator flows from the anode to the cathode electrode
- Anode electrode (F3 = left DLPFC) : ↑ cortical excitability (10-20 min stimulation → changes persists for 1 hour)

B. Assumed action?

- *Short-term*: Changes in resting membrane potential
- *After effects*: synaptic modification (NMDA-dependent mechanisms) → synaptic plasticity?

Tortella et al., 2014
Mondino et al., 2014

- **Transcranial Direct Current Stimulation (tDCS)**

C. Effects on cognition (Tortella et al., 2014):

- **8 blinded, randomized, sham-controlled studies (all targeting left BA9/46) [1-2 mA, 20 min, 5-15 sessions, 1-3 weeks]:**
  - **5 of 8 showed beneficial effects on attention and WM**
  - **Other sporadic improvements: psychomotor speed, verbal fluency, executive function**

Demirtas-Tatlidede et al., 2014 ; Mondino et al., 2014 ; Tortella et al., 2014

- **Psychotherapy**

A. CBT/Psychodynamic psychotherapy

- **Insufficient studies:**
  - **Bastos et al. (2013): 272 MDD, 2-year treatment**
    - **Psychodynamic therapy + Fluoxetine > PT > Fluox.**
  - **CBT: No study assessing cognitive effects in MDD!**

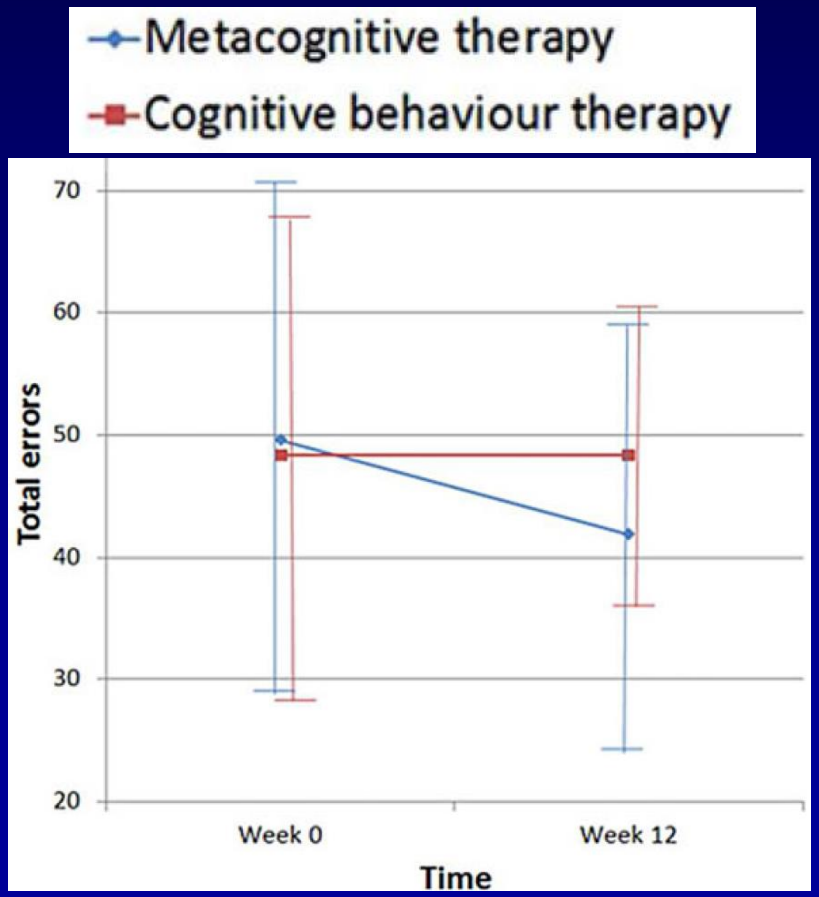
B. Metacognitive Therapy (MCT) (Wells et al.)

- **Targets: unhelpful patterns of perseverative thinking (rumination and worry), disengagement from unhealthy attentional deployment (towards threat cues)**
- **Coupled with Attentional Training (selective/divided attention, attention switching) → ↑ executive function, attentional capacity and cognitive flexibility**

- **Psychotherapy**

B. Metacognitive Theory (Groves et al., 2015)

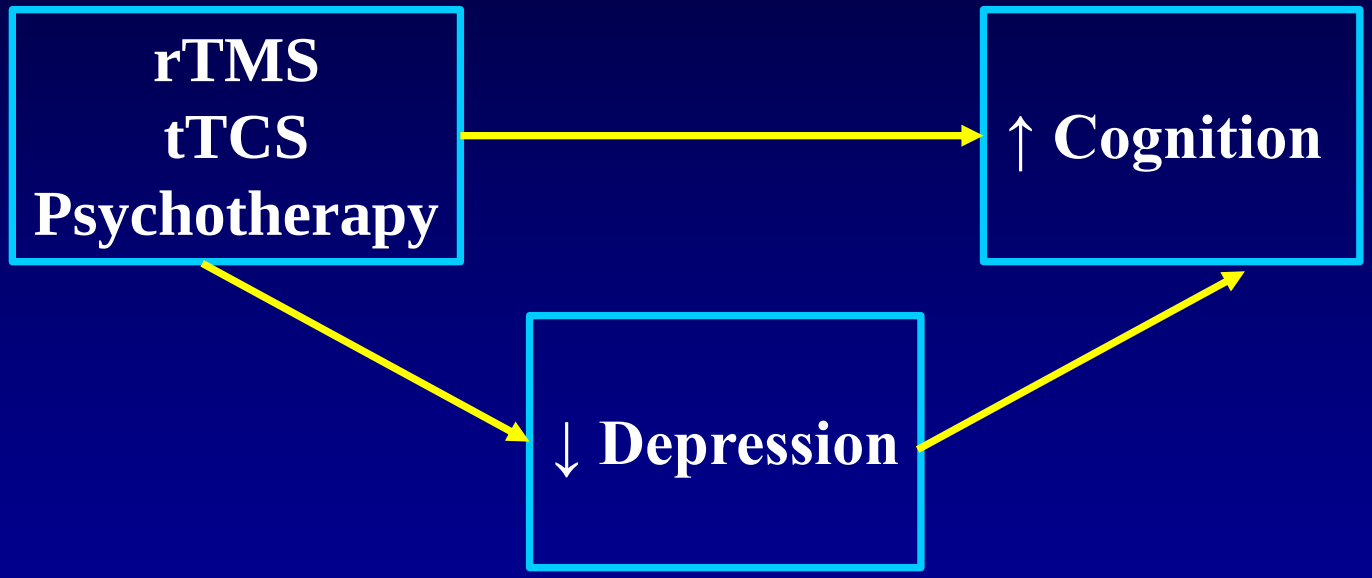
- 48 MDD individuals (all meds-free), randomized to 12-week MCT vs. CBT. Assessments after 4 and 12 weeks
- 4 weeks: ns
- 12 weeks: Spatial WM and executive function (ES: 0.77)
- Changes in cognition not correlated with changes in depressive symptoms



Groves et al., 2015

- **Unsolved Issues and Future Directions**

1. Are cognitive improvements epiphenomena secondary to symptom improvements? [Only 1 study: Nadeau et al., 2014]



***Improved design*: Assess effects on cognition after few sessions (before antidepressant effects are expected)**

→ Path (mediational) analyses

- **Unsolved Issues and Future Directions (cont.)**

2. An underappreciated issue? A single DSM item ("*diminished ability to think and concentrate*")

3. For tDCS, rTMS or psychotherapy: No meta-analyses

4. Common cognitive battery is missing (// MATRICS)

5. Prior studies have not typically corrected for multiple comparisons (up to 6-8 cognitive domains tested).

Keefe et al. (2014)'s meta-analysis: Only 12% of the analyzed cognitive tests showed a positive effect!

6. "Neuro-navigation" still rarely used ("*5 cm rule*")

7. No attempt toward "personalized" treatment (prescreening)

Demirtas-Tatlidede et al., 2014 ; Mondino et al., 2014 ; Tortella et al., 2014