Targeting Cognitive Impairment in Major Depressive Disorder - Industry Perspective

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Disclosures

- I am an employee of H. Lundbeck A/S
- I am a shareholder in H. Lundbeck A/S

Brintellix® (vortioxetine)

- Discovered and patented by H. Lundbeck A/S and co-developed with Takeda Pharmaceutical Company Ltd. for the treatment of MDD
- Approved for the treatment of MDD (FDA, US Sept. 2013) and MDE (European Commission Dec. 2013)
- Positive opinion for updating the SmPC with information on the effect of vortioxetine on certain aspects of cognitive function in MDD (European Commission Feb. 2015)

Background

Vortioxetine has a distinct mechanism of action

- Combined 5-HT receptor modulation and transporter inhibition
- Increased 5-HT, NA, DA, acetylcholine, histamine and glutamate neurotransmission, at least partly through inhibition of GABA interneurons
- Direct activity of vortioxetine at 5-HT receptors is essential for the pharmacodynamic profile of vortioxetine unlike SSRIs and SNRIs, which rely on SERT inhibition

Vortioxetine has differential effects in models of cognitive function

- Restores memory deficits due to low 5-HT or disrupted glutamatergic or cholinergic neurotransmission
- Activates cortical circuitries involved in cognitive processing (EEG)
- Restores memory deficits in old mice
- Induces dendritic branching in hippocampus
- Promotes expression of genes that regulate synaptic plasticity-related targets in frontal cortex and hippocampus
- Increases LTP in hippocampus (neuroplasticity) and increases pyramidal neuron firing in the rat mPFC

Vortioxetine modulates neural responses using fMRI during cognitive performance

- Across a circuit subserving working memory (N-Back task) in a direction opposite to the increases in BOLD-signal described in MDD
- In patients remitted from depression and healthy controls supporting direct effects on cognitive function unconfounded by syndromal depression

Sanchez et al. *Pharmacol Ther.* 2014; Leiser et al. *Neuropsychopharm*. 2012; Wallace et al. *Int J Neuropsychopharmacol*. 2014; Pehrson and Sanchez *CNS Spectr.* 2014; Pehrson et al. *Eur Neuropsychopharmacol.* 2013; Mørk et al. *J Pharmacol Exp Ther*. 2012; Riga et al. *Eur Neuropsychopharmacol.* 2013; Pehrson et al. *Eur J Pharmacol.* 2014; Dale et al. *J Psychopharmacol*. 2014; Browning et al. Neuropsychopharm 2014.

Approach

To demonstrate that

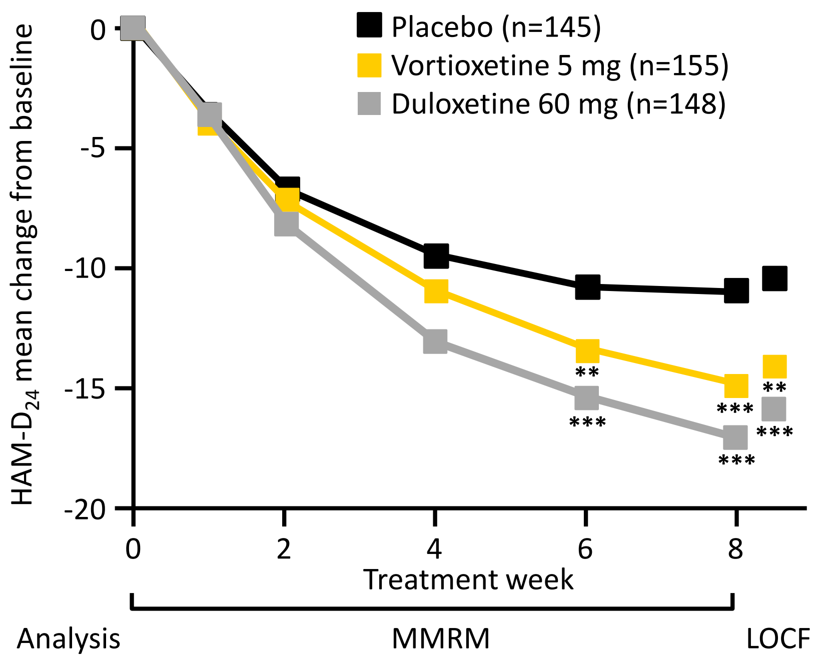
- vortioxetine's effect occurs through improvement in cognitive dysfunction in addition to alleviation of depressive symptoms in MDD
- the improvement in cognitive dysfunction is specific to vortioxetine, and not just an additional outcome of an antidepressant effect achieved by other antidepressants

First Clinical Evidence

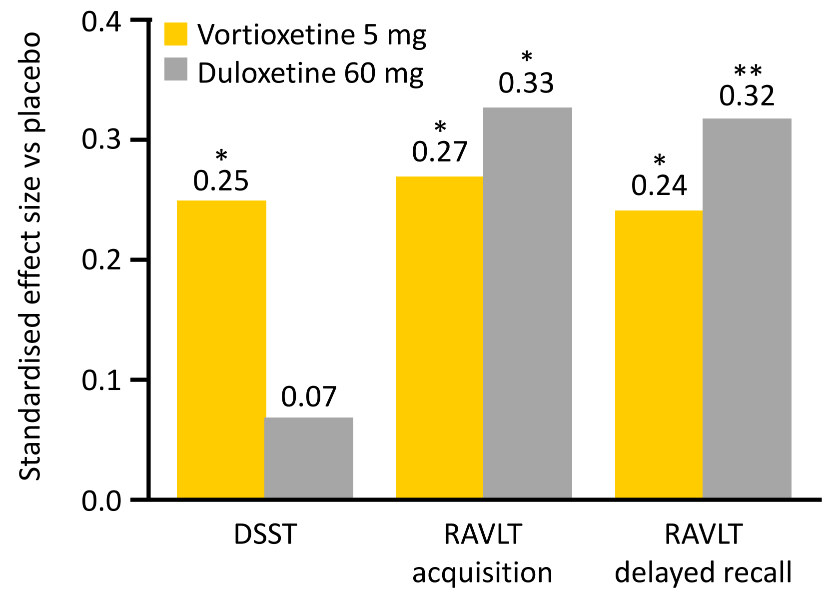
Elderly

- Vortioxetine 5 mg/day improved cognitive performance as measured by the DSST and RAVLT tests[1]
    - Cognition was a secondary endpoint
    - Key cognitive processes are involved in DSST and RAVLT e.g. executive function, working memory and attention
- Duloxetine (active reference) only improved cognitive performance in RAVLT and not in DSST
    - Confirms published data in both tests[2]

Depressive symptoms



Cognitive dysfunction[a]



[a]Compared to placebo

DSST=Digit Symbol Substitution Test
RAVLT=Rey Auditory Verbal Learning Test

1. Katona et al. Int Clin Psychopharmacol 2012;27(4):215

2. Raskin J et al. Am J Psychiatry 2007;164:900

(Elderly: NCT00811252)

Approaches to Address Specificity

- To show significant separation on measures of cognitive function that is not seen with other antidepressants despite alleviation of depressive symptoms
- Applying mediation analysis to decompose correlations and assess the extent of an independent effect on cognitive performance that is not mediated solely through an improvement in depressive symptoms

Patient Population

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- The patient has MDD, diagnosed according to DSM-IV-TR^{TM} recurrent MDD
- The patient has a MADRS total score ≥ 26
- The patient has had the current MDE for ≥3 months
- The patient is aged ≥ 18 and ≤ 65 years

(FOCUS: NCT01422213; CONNECT:NCT01564862)

Study Design Considerations (Endpoints)

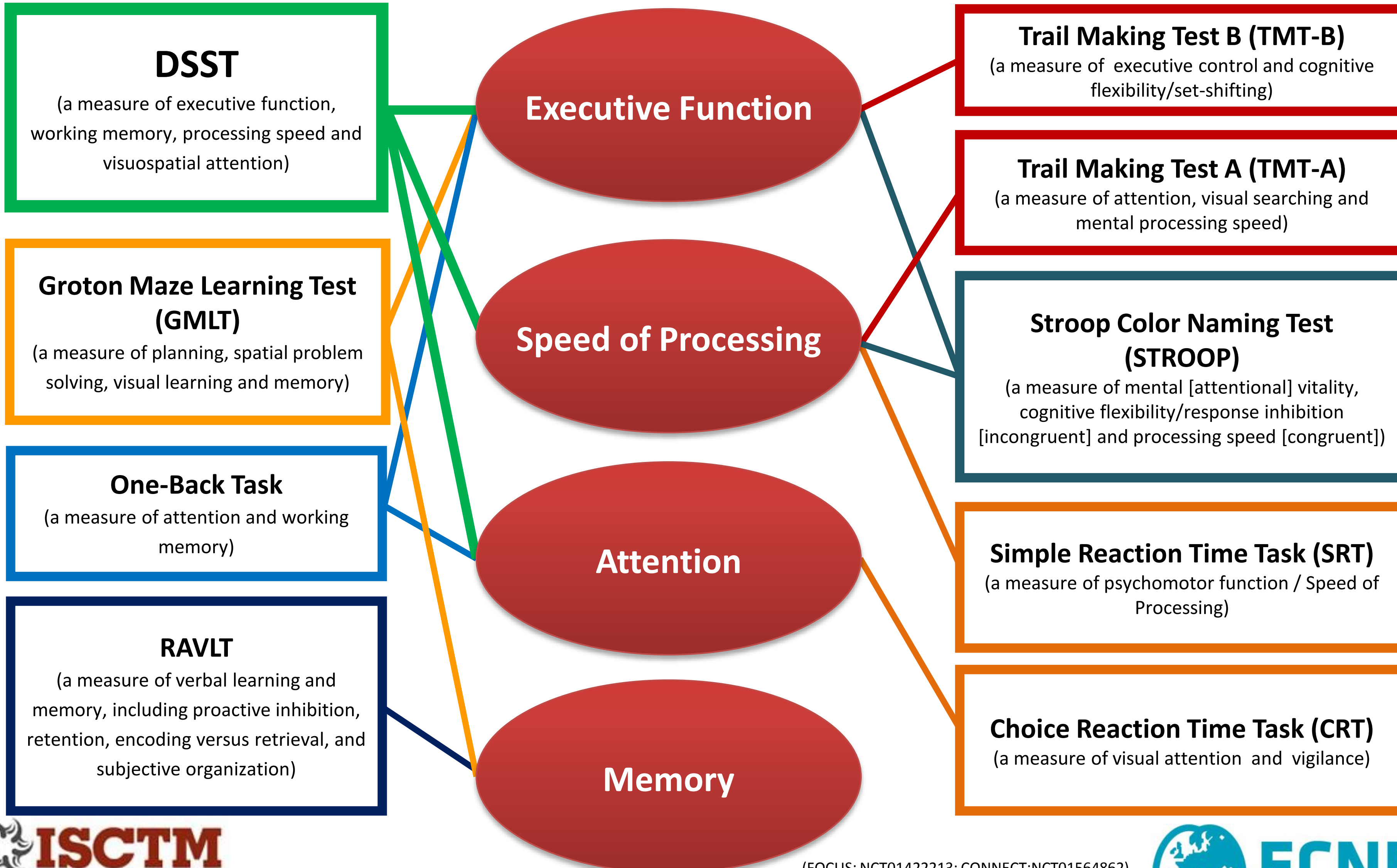
- Primary endpoint
- Sensitivity to change
- Standardised effect size
- Clinical relevance
- Specificity (influence of mood)
- Study burden

Cognitive function		
Objective	Subjective	
Neuropsychological tests	Cognitive symptoms	
	Rating scales	Questionnaires
Patient performance	Clinician rated	Patient rated

Functionality		
Objective	Subjective	
Performance-based assessment of functional skills	Rating scales	Questionnaires
Patient performance	Clinician rated	Patient rated

(FOCUS: NCT01422213; CONNECT:NCT01564862)

Study Design Considerations (Test Selection Strategy)



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(FOCUS: NCT01422213; CONNECT:NCT01564862)

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DSST

- The Digit Symbol Substitution Test (DSST) is an objective neuropsychological test of executive function, working memory, processing speed and visuospatial attention
- Requires the integrity of a broad range of domains relevant for MDD
- Shares significant variance with cognitive test batteries as well as measures of functional capacity
- Used for more than 30 years with different age groups and found to be a predictor of outcome in patients with severe mental illness

➢ *DSST is an integrated measure incorporating multiple cognitive abilities*

Supportive Evidence

- The effect on DSST was supported by the significant effect on tests measuring other specific domains

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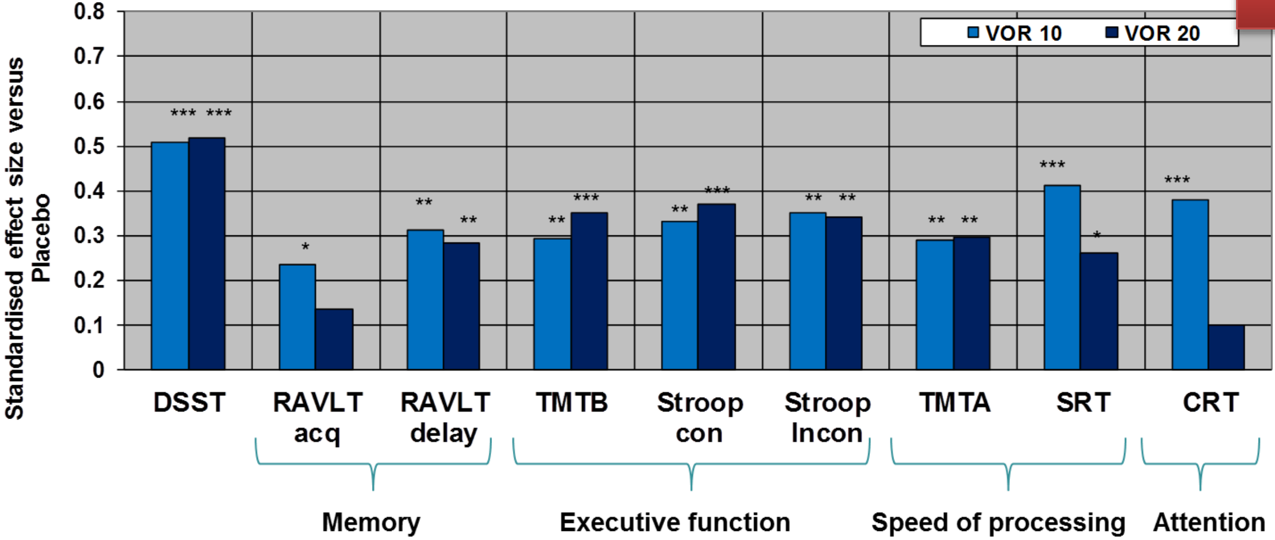


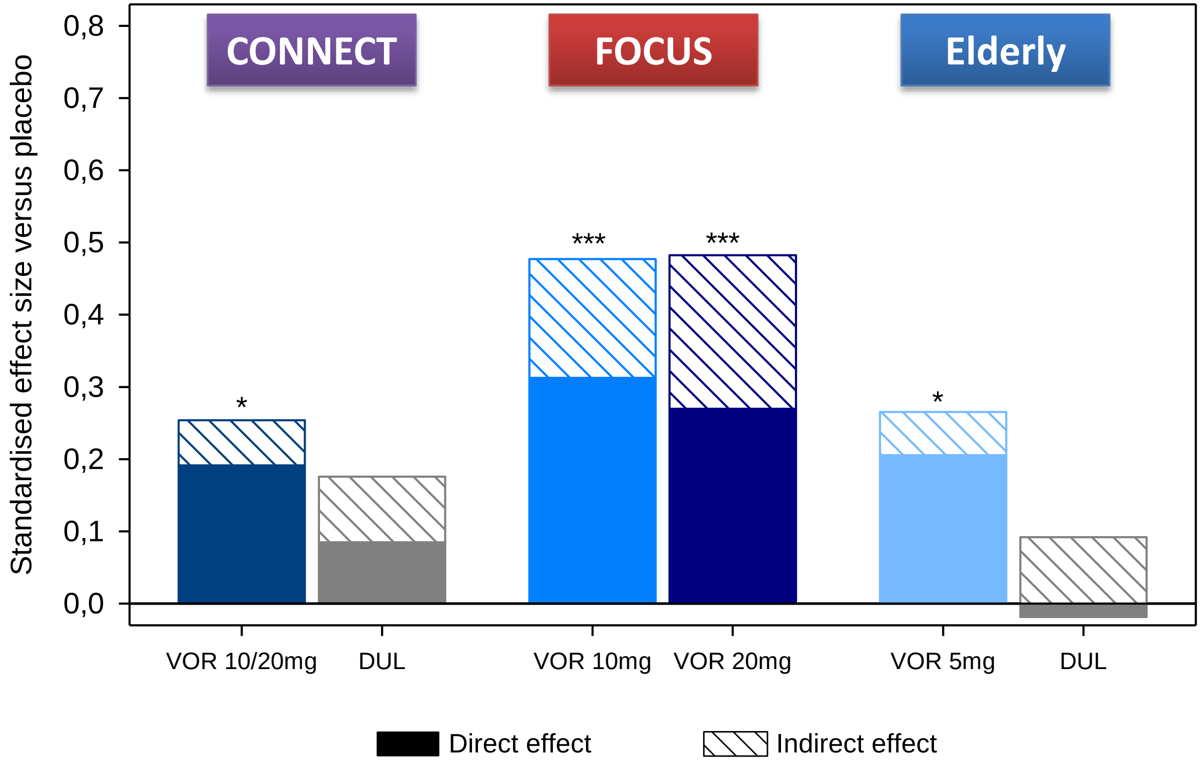
McIntyre et al. *Int J Neuropsychopharmacol*. 2014 Oct;17(10):1557-67

➢ *DSST considered appropriate as primary endpoint and applied in the following study for replication*

(FOCUS: NCT01422213)

DSST - Replication

DSST *Number of Correct Symbols*, Change from Baseline at Week 8 (FAS, ANCOVA, LOCF, Path Analysis)



Path Analysis mediated via MADRS Total Score

- The effect of vortioxetine on DSST performance is not mediated solely through an improvement in general depressive symptoms

(CONNECT: NCT01564862, Mahableshwarkar et al. CINP. 2014; FOCUS: NCT01422213, McIntyre et al. *Int J Neuropsychopharmacol*. 2014 ; Elderly: NCT00811252, Katona et al. *Int Clin Psychopharmacol.* 2012)

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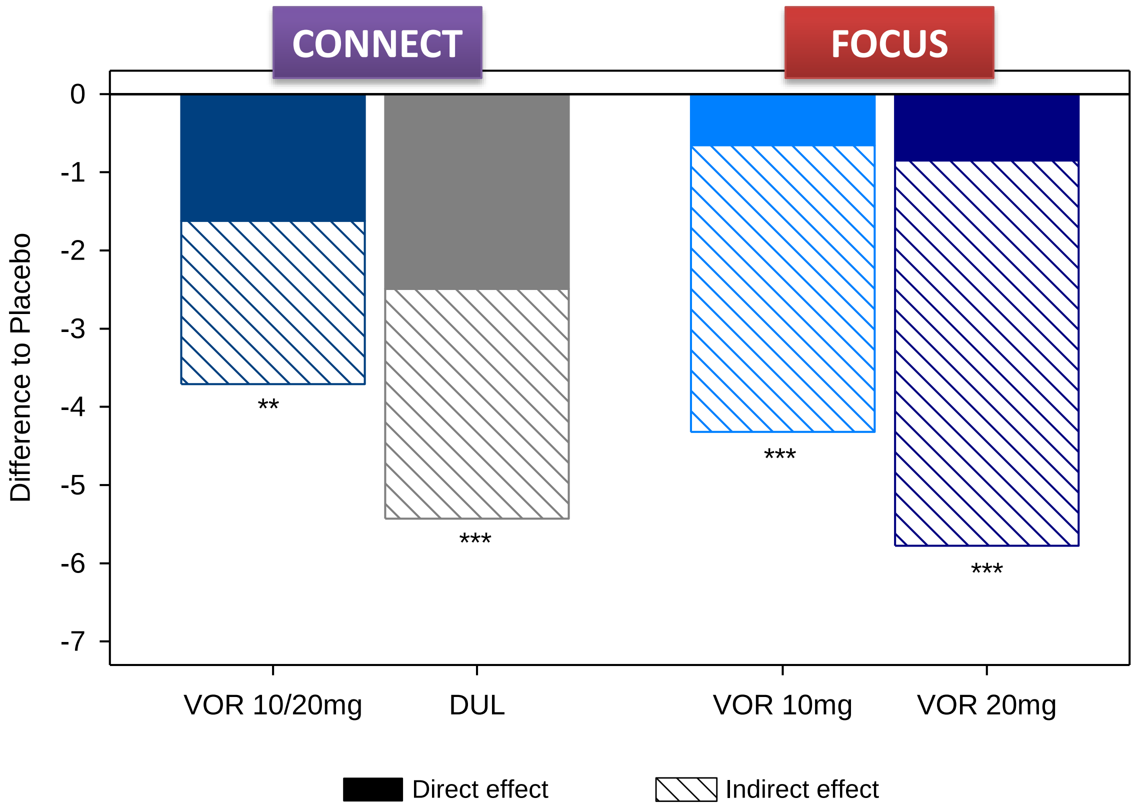
Patient Perception (PDQ)

PDQ Total Scores, Change from Baseline at Week 8 (FAS, ANCOVA, LOCF, Path Analysis)



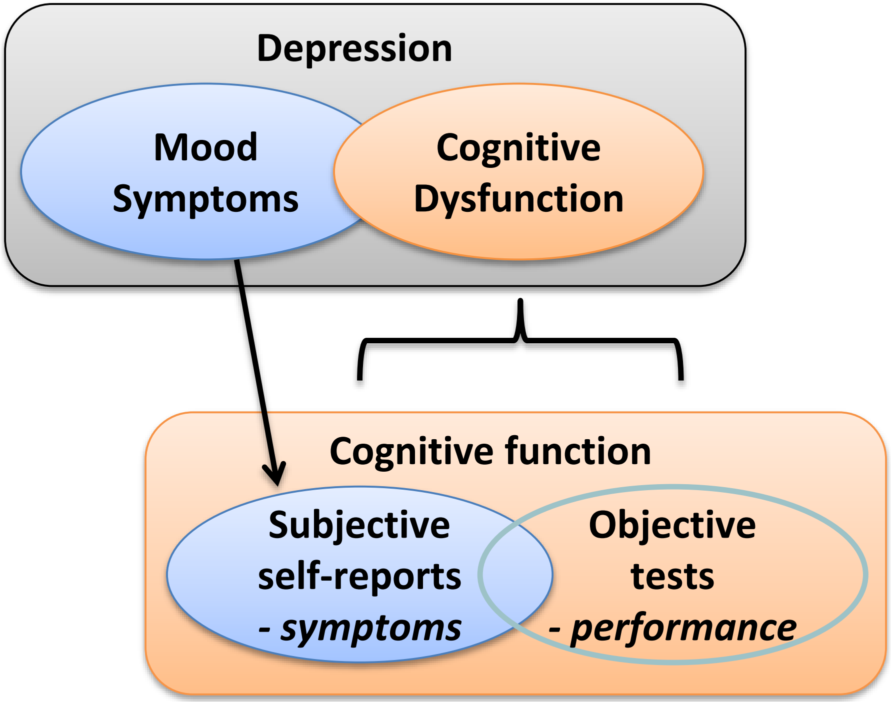
Path Analysis mediated via MADRS Total Score

- The effects on the subjective measure of cognitive function were found to a large degree to be attributable to the improvement in general depressive symptoms

(CONNECT: NCT01564862, Mahableshwarkar et al. CINP. 2014; FOCUS: NCT01422213, McIntyre et al. *Int J Neuropsychopharmacol*. 2014)

PDQ=Perceived Deficits Questionnaire

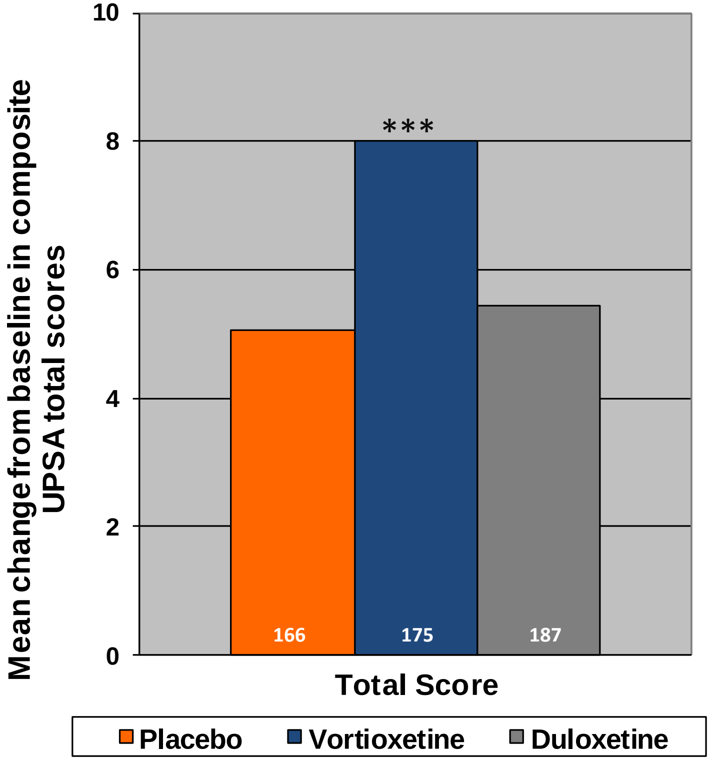
Framework



- Objective measures of cognitive dysfunction are needed to disentangle the effect on cognitive dysfunction in the presence of mood symptoms

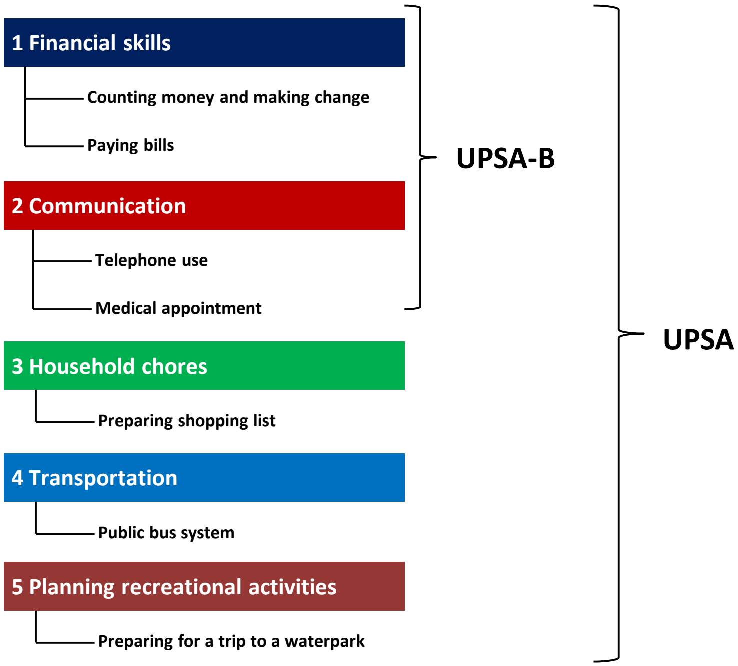
UPSA – Functional Capacity

CONNECT



p-value: ***<0.001 vs placebo

The **UPSA** evaluates the abilities of an individual to perform everyday tasks that are considered necessary for independent functioning in the community



- Objective performance-based measures capture effects not addressed by depression scales, which are primarily designed to assess mood symptoms

(CONNECT: NCT01564862, Mahableshwarkar et al. CINP. 2014)

UPSA=University of California, San Diego, Performance-Based Skills Assessment

Targeting Cognitive dysfunction in MDD

A perspective from the vortioxetine program

- Cognitive dysfunction is a distinct dimension of depression
- Studying the acute MDD population allows to evaluate the therapeutic effect in relation to both the mood and the cognitive components of depression
- Objective measures of cognitive function capture therapeutic effects not addressed by depression scales that primarily are designed to assess changes in mood symptoms
- Improvement on objective measures of cognitive function translates into improved functional capacity
- Patient's perception, although relevant, is highly influenced by mood and is therefore less distinct
- Cognitive dysfunction in MDD can be specifically targeted by demonstrating effect on objective measures of cognitive function not achieved by other antidepressants