Objective Measures of Cognitive Impairment in Depression

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Disclosures

- Grants — Wellcome Trust
- Honoraria — AstraZeneca, BMS, Lundbeck, Medscape, Otsuka, Servier, Takeda
- Shares — P1vital
- Paid positions — University of Oxford
- Advisory boards — AstraZeneca, BMS, Teva Lundbeck, Medscape, Otsuka, P1Vital, Servier, Sunovion, Takeda

Objectives

- Cognition and depression
  - Cogito ergo sum
- What domains are impaired in MDD?
- What measures
- Role of fMRI

DSM-IV Major Depressive Episode

(1) depressed mood

(2) markedly diminished interest or pleasure

(3) significant weight loss

(4) insomnia or hypersomnia

(5) psychomotor agitation or retardation

(6) fatigue or loss of energy

(7) feelings of worthlessness or excessive or inappropriate guilt

(8) diminished ability to think or concentrate, or indecisiveness

(9) recurrent thoughts of death, suicidal ideation etc

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How to measure cognition

- Proximally
  - Actual current ***objective performance on a relevant task***
  - Current subjective perception
- More distally
  - Symptom scales, quality of life
- Most distally
  - Function, return to work

Depression ***and Cognitive Impairment***

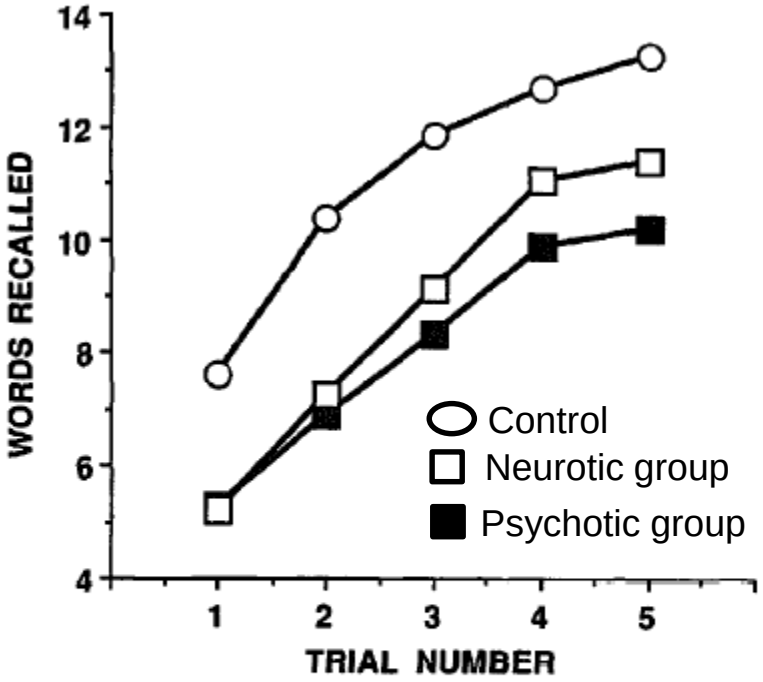

Fig. 1. The mean number of words recalled on successive trials of the AVLT by control (open circles), neurotic (open squares) and psychotic (closed squares) groups. Repeated measures ANOVA showed a main effect of group ($F(2, 57) = 12.1$, $P = 0.000$). The patient groups were clearly different from controls but not from each other. Further details in text and Table 2.

- List learning in 2 groups of depressed patients and controls
- Both endogenous and neurotic groups impaired
- Other domains also implicated
- Related to depression severity

Austin et al. 1992JAD, 25, 21–29. doi:10.1016/0165-0327(92)90089-O

Impaired Cognition

	Endogenous (20)	Neurotic (20)	Control (20)	*P* value for F test	Scheffe ($P < 0.05$)
Sum 5 AVLT Trials	40.5 (12.0)	44.0 (8.2)	55.8 (11.2)	0.0001	C > N, E
Delayed Recall	8.0 (3.5)	9.2 (4.0)	12.2 (2.9)	0.002	C > N, E
Recognition	9.2 (3.6)	9.4 (6.3)	13.4 (1.9)	0.004	C > N, E
'Forgetting'	2.3 (1.7)	2.4 (2.3)	1.5 (1.5)	0.21	
Digitspan (forward)	9.3 (2.0)	8.8 (1.7)	9.2 (1.9)	0.66	
Digitspan (back)	7.0 (2.2)	6.4 (2.1)	7.8 (2.2)	0.19	
Block design	23.9 (12.8)	29.8 (10.2)	32.1 (11.1)	0.12	
DSST	37.9 (15.0)	45.9 (12.8)	53.7 (10.6)	0.001	C > E
Trails A (secs)	50.7 (24.5)	40.9 (10.1)	35.8 (11.9)	0.02	C < E
Trails B (secs)	144 (85.1)	100.3 (70.3)	68.9 (22.5)	0.002	C < E
Verbal fluency (Words/min.)	12.8 (5.8)	13.2 (6.3)	15.8 (4.8)	0.23	

Scores for the three groups were compared by one way ANOVA. Differences between groups were located post hoc with the Scheffe test; abbreviations are, C = Control group, N = Neurotic group, E = Endogenous group.

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Sum 5 AVLT Trials	40.5 (12.0)	[illegible] (8.2)	55.8 (11.2)	0.0001	C > N, E
Delayed Recall	8.0 (3.5)	[illegible]	[illegible]	0.002	C > N, E
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Memory

Speed

Scores for the three groups were compared by one way ANOVA. Differences between groups were located post hoc with the Scheffe test; abbreviations are, C = Control group, N = Neurotic group, E = Endogenous group.

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Time of day matters

8AM v 8PM

Melancholic patients

Table 2

	Morning		P	Evening		P
	Melancholic	Control		Melancholic	Control	
Mental state						
BFS mood scale [a]	39.7 (9.6)	3.8 (3.9)	0.000	25.1 (14.8)	4.8 (4.7)	0.000
APSAQ	18.8 (7.1)	5.9 (4.2)	0.000	15.3 (6.0)	5.8 (4.3)	0.000
Isometric contraction (kg) [a,e]	23.6 (7.5)	35.3 (10.6)	0.000	28.4 (7.6)	34.3 (10.0)	0.05
Attention/concentration						
Digits forward [a,d]	6.6 (1.1)	8.3 (0.8)	0.000	7.7 (1.1)	7.4 (1.4)	NS
Digits backward [a]	4.6 (1.1)	5.6 (1.6)	0.02	5.5 (1.2)	5.5 (1.6)	NS
Psychomotor speed						
Digit symbol substitution [b]	40.0 (15.9)	61.1 (13.1)	0.000	46.0 (15.1)	59.5 (12.9)	0.004
Reaction latency (ms)	561.4 (150.1)	443.9 (77.3)	0.004	529.3 (149.2)	448.3 (98.2)	NS
Movement latency (ms)	428.1 (157.1)	333.0 (90.4)	0.03	403.6 (124.3)	343.9 (112.5)	NS
Total latency (ms)	717.7 (197.8)	576.7 (120.4)	0.01	674.1 (184.9)	573.4 (136.2)	NS
Memory–AVLT						
Immediate (AVLT-1) [b,c]	5.3 (1.8)	7.7 (2.2)	0.001	6.2 (1.9)	6.2 (2.5)	NS
Learning (AVLT-5) [b]	9.2 (2.6)	13.6 (1.9)	0.000	11.1 (3.0)	12.5 (2.5)	NS
AVLT total [b,f]	38.7 (11.2)	55.4 (9.8)	0.000	44.5 (12.5)	49.9 (11.9)	NS
Second list (AVLT-6)	4.2 (1.9)	5.2 (2.0)	NS	4.6 (1.8)	5.5 (1.8)	NS
Delay (AVLT VI) [b]	6.5 (3.3)	11.6 (3.4)	0.000	9.2 (3.8)	10.2 (3.6)	NS
30-min delay [c]	5.2 (3.6)	11.4 (3.4)	0.000	7.7 (4.1)	9.9 (4.0)	NS
Recognition	6.6 (4.9)	12.3 (4.3)	0.000	9.4 (5.1)	11.2 (4.4)	NS
Memory–delayed match-to-sample (ms)						
Simultaneous	4052.3 (1796.6)	2675.7 (707.6)	0.004	3509.0 (1244.2)	2638.5 (618.8)	0.009
0 s	3468.1 (1036.9)	2473.6 (931.8)	0.03	3083.8 (873.4)	2821.6 (1038.2)	NS
4 s	3619.2 (1188.7)	2965.1 (757.0)	0.05	3442.4 (989.5)	2933.5 (909.3)	NS
12 s	4565.5 (1745.1)	3524.3 (1020.4)	0.03	4257.3 (1704.1)	3461.2 (1060.9)	NS
Total correct	31.1 (4.8)	35.8 (3.6)	0.002	32.0 (4.6)	34.8 (3.8)	0.04

Comparison of morning and evening test scores (mean ± SD) between melancholics and controls. Repeated measures multivariate ANOVA shows a significant interaction between diagnosis, type of test and time of testing ($F_{4,94}$, df 20, $P = 0.001$). P values presented in the table represent between-group comparisons, with t tests (2-tailed). Within-subject scores are compared with paired t tests (2-tailed) and show significant morning/evening changes in the melancholics ([a] $P \leq 0.001$, [b] $P \leq 0.01$, [c] $P \leq 0.05$) and in controls ([d] $P \leq 0.001$, [e] $P \leq 0.01$, [f] $P \leq 0.05$).

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Choice of test

- No evidence for specificity
- Execution, Working memory, Speed
  - Slowing clearly a core symptom
- Practicality – pencil and paper or computer
- Time of day
- Fatigue – don’t use a battery if you dont have to
- Test/retest and learning

Digit symbol substitution test

- DSST – cue: digit-symbol pairs (e.g. 1/_,... 7/Λ,8/X,9/=)

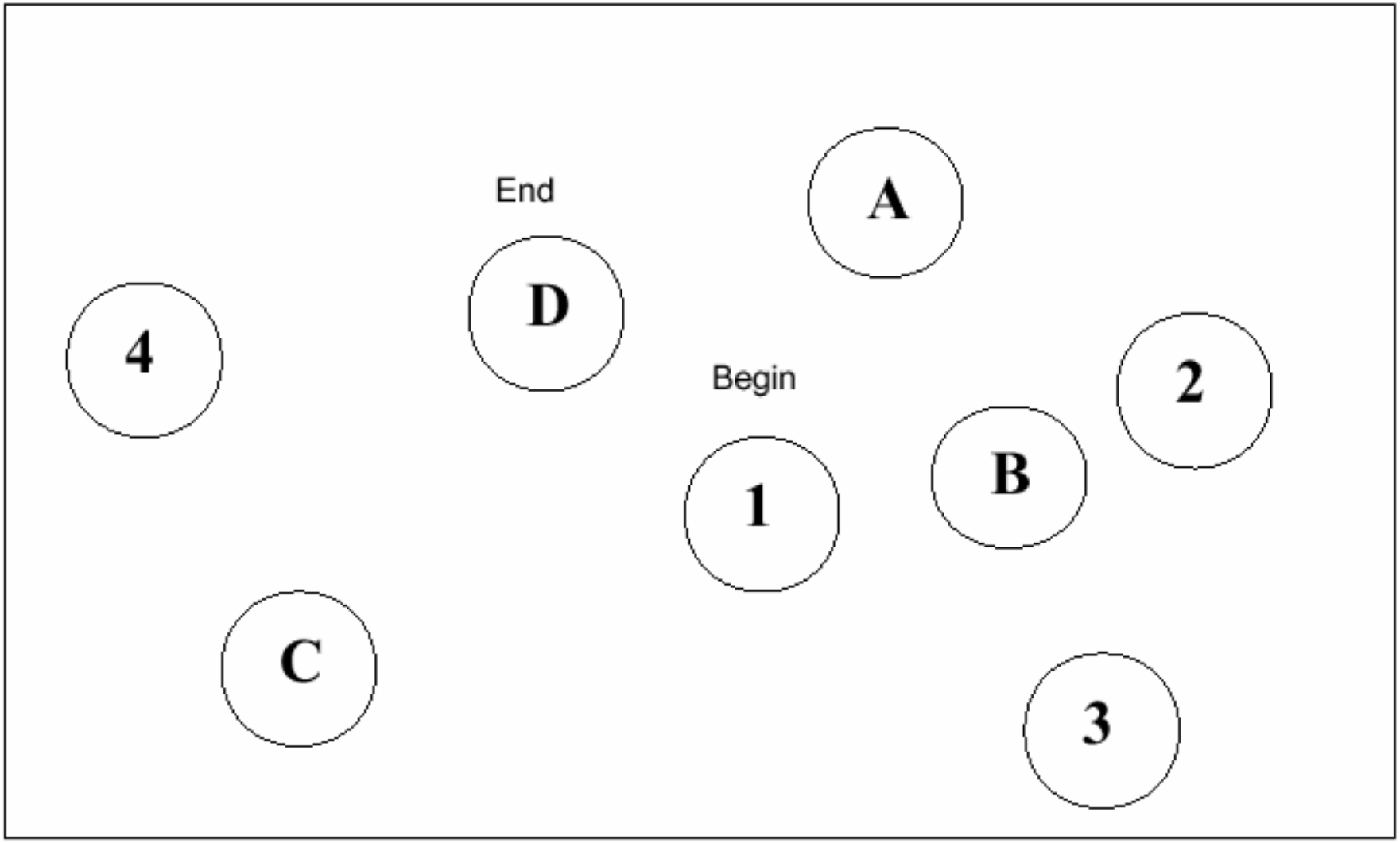
  Response: list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible.

Digit	1	2	3	4	5	6	7	8	9
Symbol	—	†	Π	L	Γ	o	∧	X	=

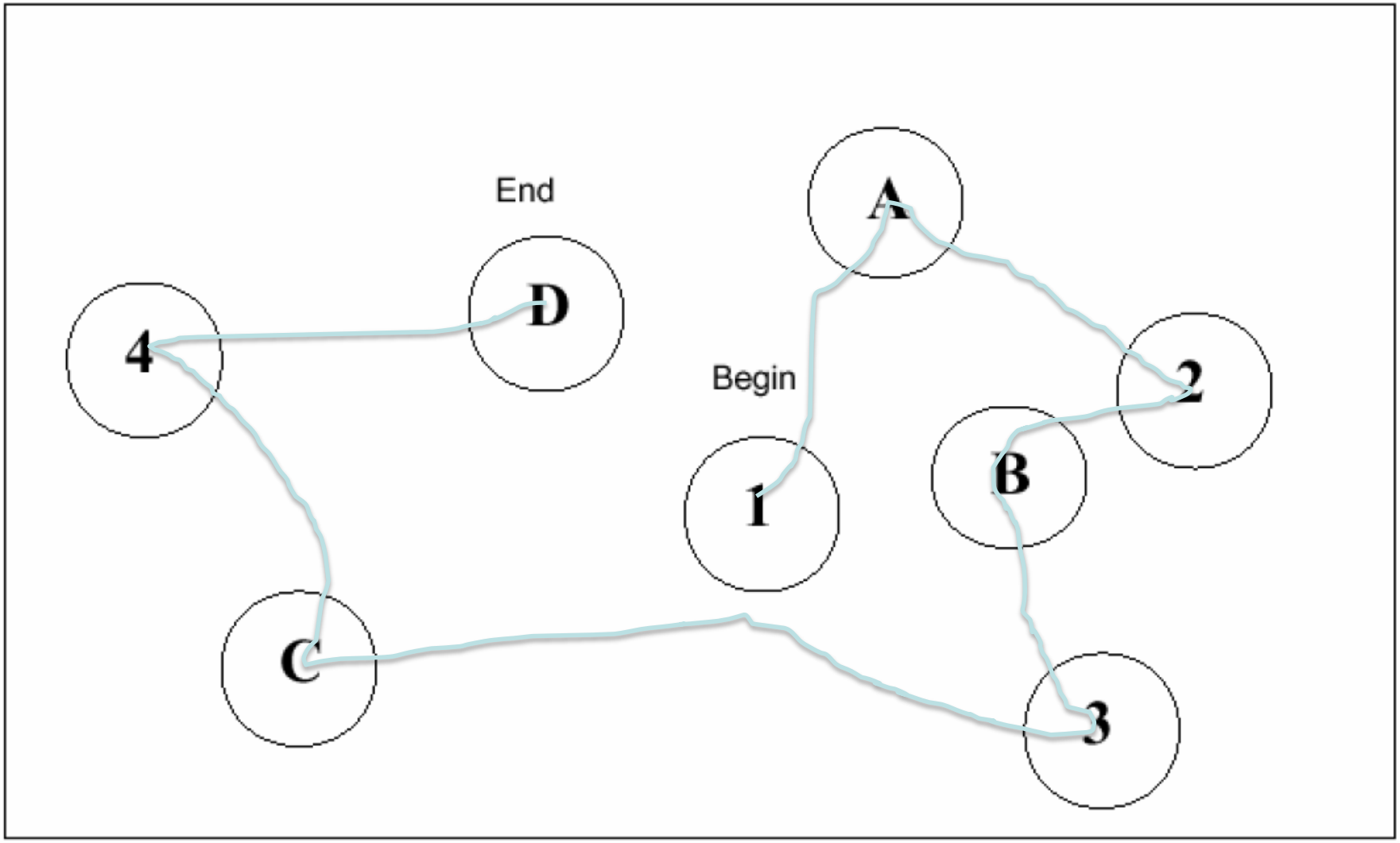
Example

Digit	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1
Symbol	—	Π	∧	†	L	x																	

Trail Making Test Part B – *SAMPLE*



Trail Making Test Part B – *SAMPLE*



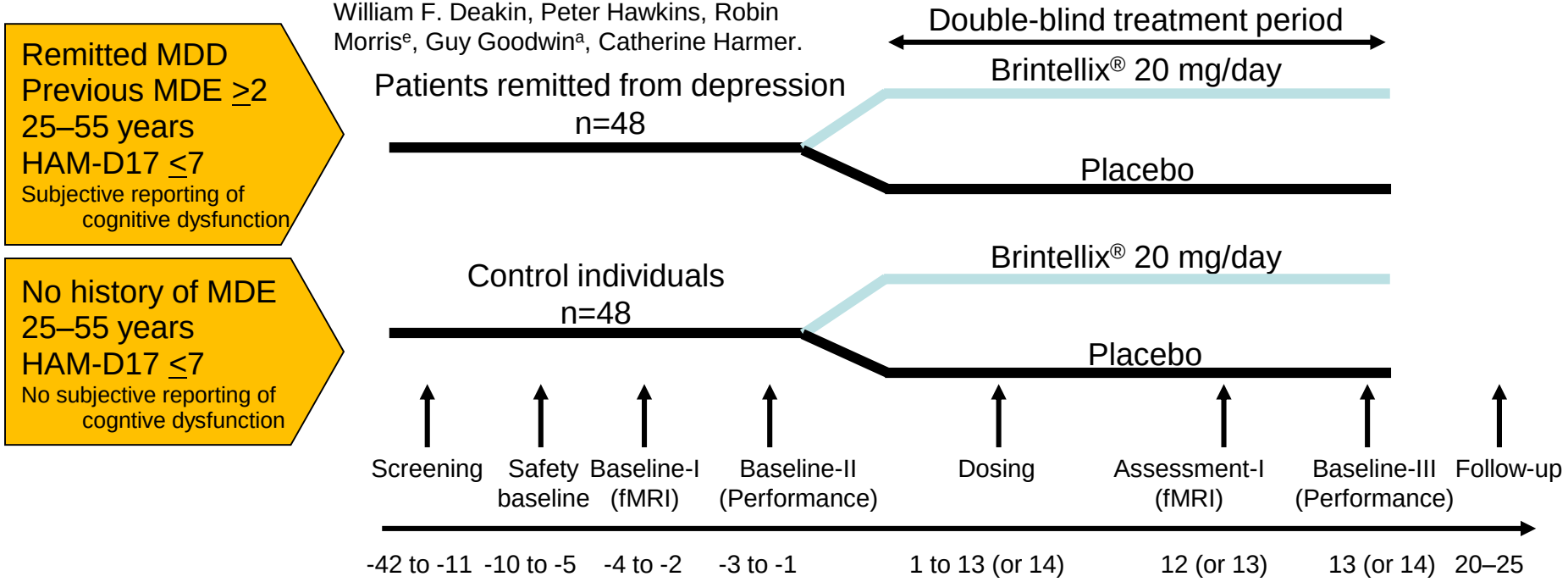
Objective surrogate measures of cognitive impairment

Use of fMRI

- Excellent where behaviour/processing not observable
- Tends to be more sensitive than behaviour
- Many examples where patients different from controls at baseline
- Multiple centres gets difficult

Bold fMRI signals in subjects remitted from depression and controls - Study design

Jessica Smith, Michael Browning, Silke Conen, Richard Smallman, Jeppe Buchbjerg, Klaus Groes Larsen, Christina Kurre Olsen, Søren Rahn Christensen, Gerard R. Dawson, William F. Deakin, Peter Hawkins, Robin Morris[e], Guy Goodwin[a], Catherine Harmer.

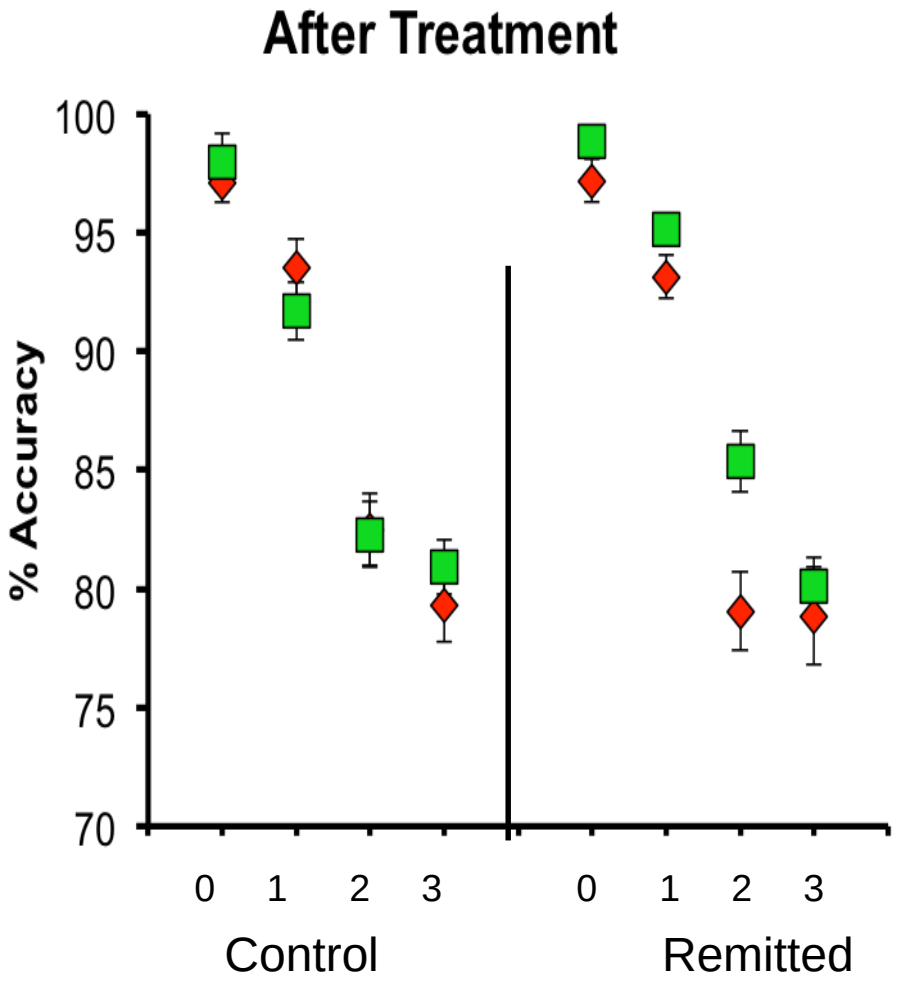


Primary end point:

- BOLD fMRI signal in brain areas associated with executive function (working memory), specifically the prefrontal cortex and anterior cingulate during performance of the N-back task

- Number of patients: 24 per treatment arm
- fMRI and cognitive assessments at baseline and Week 2

N-Back performance



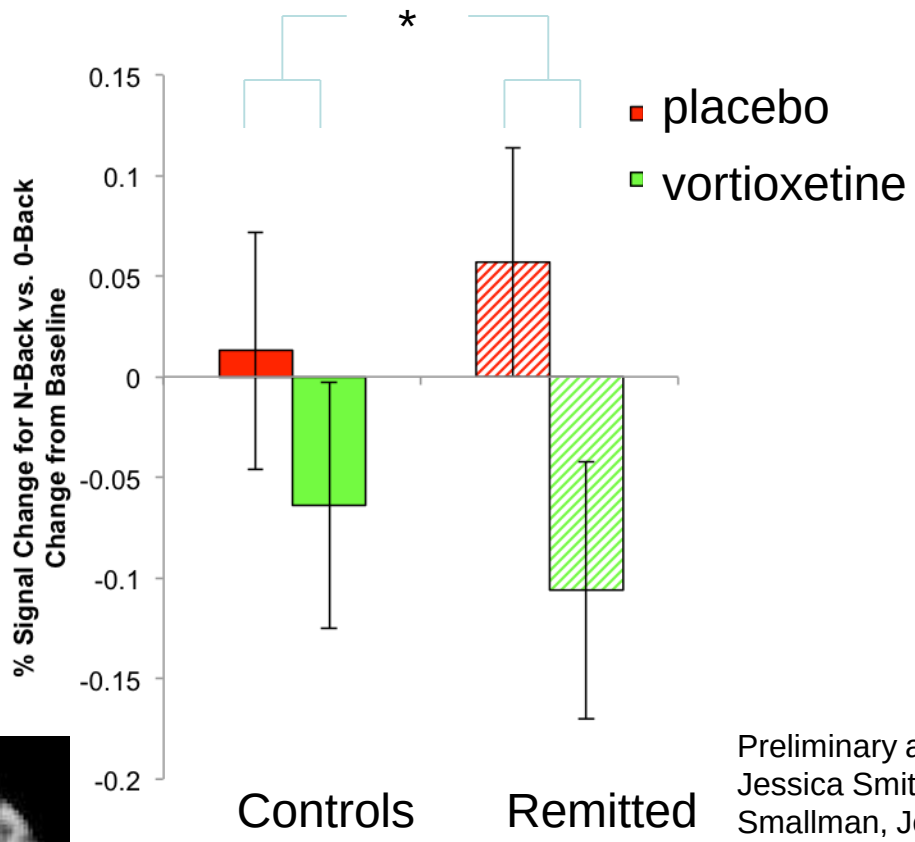
Placebo
Vortioxetine

Preliminary analysis of data now in submission
Jessica Smith, Michael Browning, Silke Conen, Richard Smallman, Jeppe Buchbjerg, Klaus Groes Larsen, Christina Kurre Olsen, Søren Rahn Christensen, Gerard R. Dawson, William F. Deakin, Peter Hawkins, Robin Morris[e], Guy Goodwin[a], Catherine Harmer.

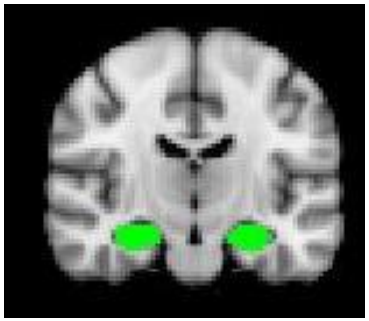
No effect of drug on accuracy [p>0.2]

Vortioxetine reduces left hippocampal activity in N-Back task (ROI analysis)

Left hippocampus ROI



In regions previously reported to be hyperactive in patients with depression vortioxetine significantly reduces neural activity while performing the N-back task in subjects remitted from their depression



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CONCLUSIONS

- Cognition and depression
  - Clearly associated and important
- What domains? What measures?
  - Multiple, so choice of tests pragmatic
- Challenge is pseudospecificity
- Validation: MR

The end