Newcastle University
Institute of Neuroscience

NCMD
Northern Centre for Mood Disorders

Cognition in Mood Disorders

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The Queen's Anniversary Prizes
For Higher and Further Education
2013

Mood disorders research – a global effort …

Cognitive function in major depression

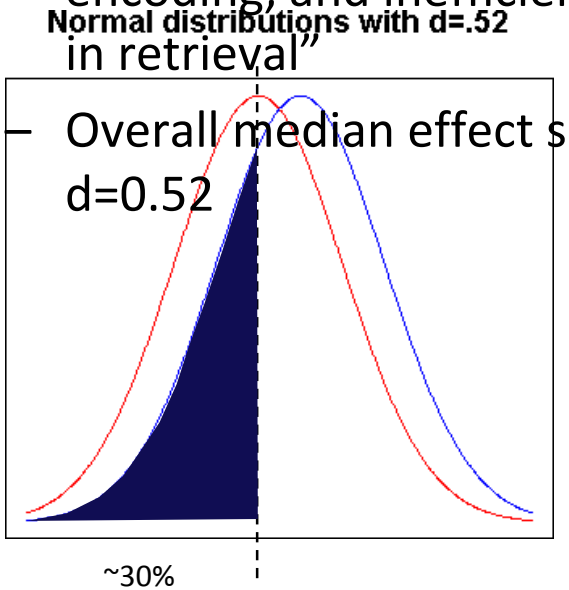
z	Percentile standing	d	Cohen's U_1	*Non-overlap (%)	*Overlap (%)
0.0	50.0	**0.0**	0.0	0.0	100.0
-0.1	46.0	**0.1**	7.7	4.0	96.0
-0.2	42.0	**0.2**	14.7	8.0	92.0
-0.3	38.0	**0.3**	21.3	11.9	88.1
-0.4	34.0	**0.4**	27.4	15.8	84.2
-0.5	31.0	**0.5**	33.4	19.7	80.3
-0.6	27.0	**0.6**	38.2	23.6	76.4
-0.7	24.0	**0.7**	43.0	27.4	72.6
-0.8	21.0	**0.8**	47.4	31.1	68.9
-0.9	18.0	**0.9**	51.6	34.7	65.3
-1.0	16.0	**1.0**	55.4	38.3	61.7
-1.1	14.0	**1.1**	58.9	41.8	58.2
-1.2	12.0	**1.2**	62.2	45.2	54.8
-1.3	10.0	**1.3**	65.3	48.4	51.6
-1.4	8.1	**1.4**	68.1	51.6	48.4
-1.5	6.7	**1.5**	70.7	54.7	45.3
-1.6	5.5	**1.6**	73.1	57.6	42.4
-3.0	0.1	**3.0**	92.8	86.6	13.4
-3.2	<0.1	**3.2**	94.2	89.0	11.0
-3.4	<0.1	**3.4**	95.3	91.1	8.9
-3.6	<0.1	**3.6**	96.3	92.8	7.2
-3.8	<0.1	**3.8**	97.0	94.3	5.7
-4.0	<0.1	**4.0**	97.7	95.5	4.5

← 'small'

← 'medium'

← 'large'

- Meta analyses
- Zakzanis et al (1998)
  - 22 studies
  - 1980 onwards, all patients with DSM-III-R diagnosed MDD
  - "dysfunction of effortful encoding, and inefficiency in retrieval"
  - Overall median effect size d=0.52



* Grice, J. W., & Barrett, P. T. (2011). *A note on Cohen's overlapping proportions of normal distributions*. Stillwater, OK: Oklahoma State University, Dept. of Psychology.

McGough, J. J. & Faraone, S. V. (2009). Estimating the size of treatment effects: moving beyond p values. *Psychiatry, 6(10),* 21-9.

Zakzanis, K. K. (2001). Statistics to tell the truth, the whole truth, and nothing but the truth: Formulae, illustrative numerical examples, and heuristic interpretation of effect size analyses for neuropsychological researchers. *Archives of Clinical Neuropsychology, 16*(7), 653-667.

Cognitive function in major depression

- Demographic and clinical correlates
  - Age
  - Hospitalisa
  - Severity
  - Episode re
  - Medicatior

	MDD vs Controls	
	Mean effect (d)	k
Age of participants		
Over 60 years	0.60	39
Under 60 years	0.45	97
Hospitalisation		
Inpatient	0.59	84
Outpatient	0.18	30
ECT		
Yes	1.62	3
No	0.37	46
Severity of depression		
Mild	0.21	5
Moderate	0.62	15
Severe	0.41	7

Christensen et al (1997)

BRITISH JOURNAL OF PSYCHIATRY (2003), 182, 214–220

Neurocognitive impairment in drug-free patients with major depressive disorder

RICHARD J. PORTER, PETER GALLAGHER, JILL M. THOMPSON and ALLAN H. YOUNG

- *Aim*: To examine neuropsychological function in 44 MDD patients and 44 matched controls

  - Exclude medication effects (drug-free > 6 weeks)
  - Moderate to severe depression (HAMD > 15)
  - Outpatients only
  - No history of ECT
  - No current alcohol/substance abuse

Table 1 Demographic details for subjects with depression and for controls

	Depression			Controls		
	Mean	s.d.	Range	Mean	s.d.	Range
Age (years)	32.9	10.6	19–61	32.3	11.4	18–55
NART	107.9	10.7	85–123	109.6	7.6	89–122
Formal education (years)	13.3	2.4	10–16	14.2	1.7	11–16
Gender (male:female)		15:29			15:29	
Season[1]		9:11:16:8			7:11:19:7	
Menstrual cycle[2]		13:7:5 (3 unknown)			18:8:3	

NART, National Adult Reading Test.
1. Spring:Summer:Autumn:Winter.
2. Follicular:luteal:post-menopausal.

- Matched on all variables

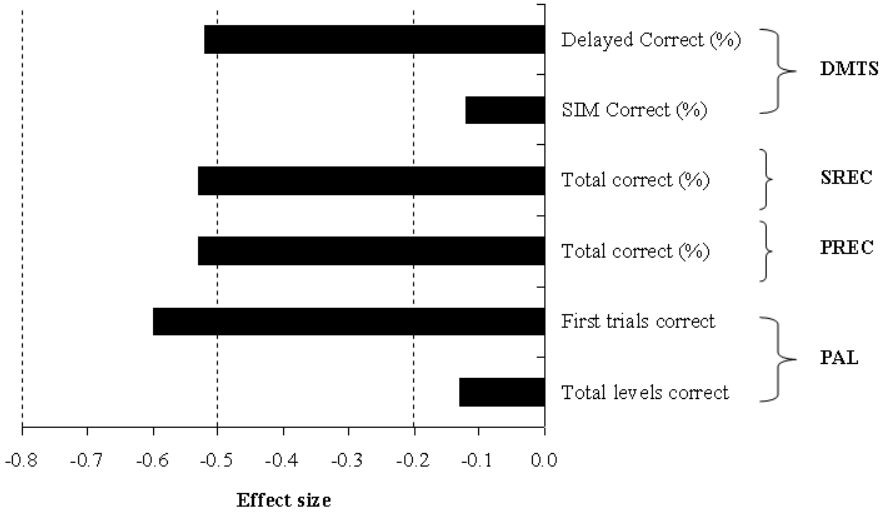
Table 2 Patients with depression: illness characteristics and rating scales

	Mean (median)	s.d.	Range
$HRSD_{17}$	21.1	4.4	15–30
MADRS	28.9	5.5	18–38
Beck Depression Inventory	27.9	10.2	8–47
Total lifetime duration (months)	17.5 (7)	29.3	2–120
Age at onset (years)	29.2	9.0	17–51
Length of current episode (months)	12.5 (6)	23.5	1–120
Duration drug-free (weeks)[1]	78.6 (48)	85.9	6–336

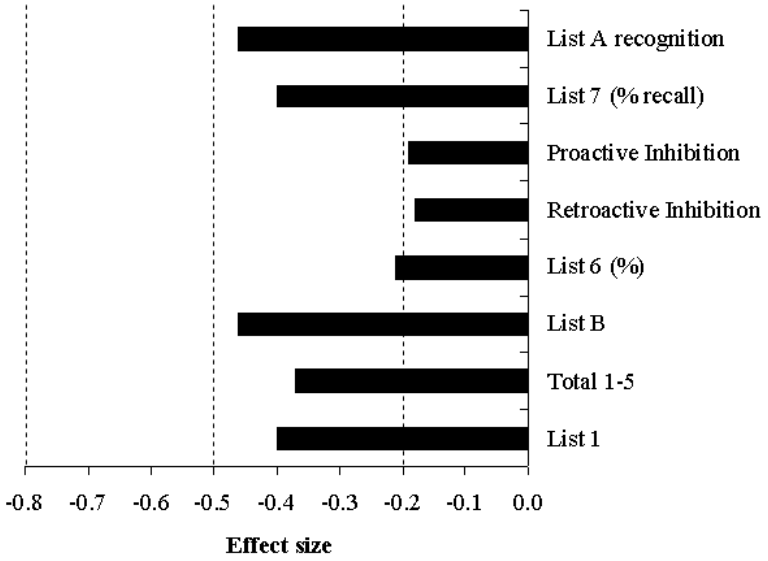
$HRSD_{17}$, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale.
1. Based on 18 patients with depression who had previously received antidepressant medication.

- n=30 (68%) were first-episode with n=11 (25%) having had one previous depressive episode and only n=3 (7%) having had 2 or more.
- n=26/44 (59%) drug naive

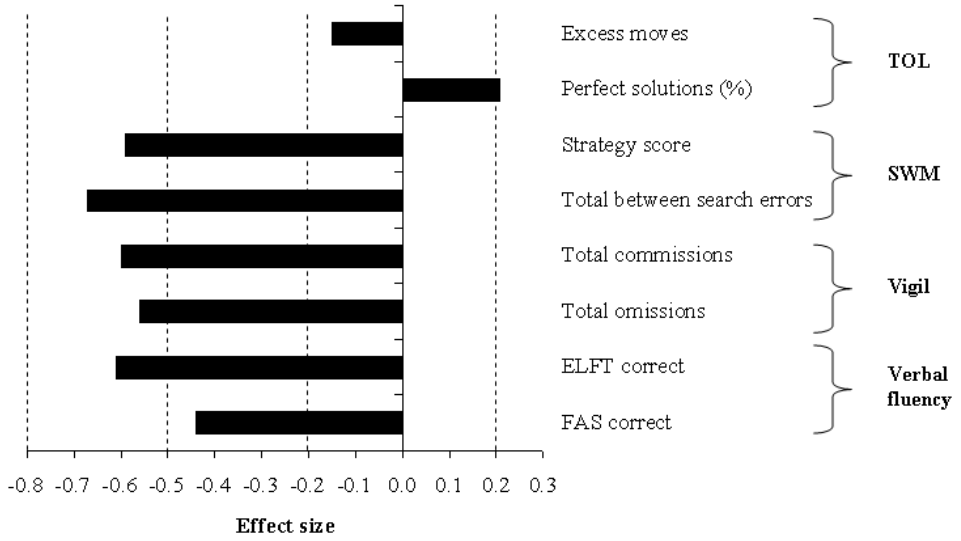
Visuo-spatial



Verbal



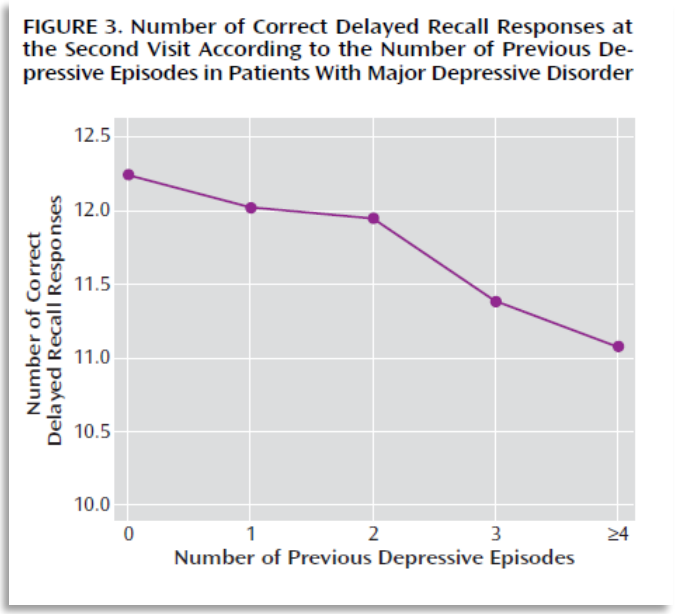
Attention and executive functions



Summary

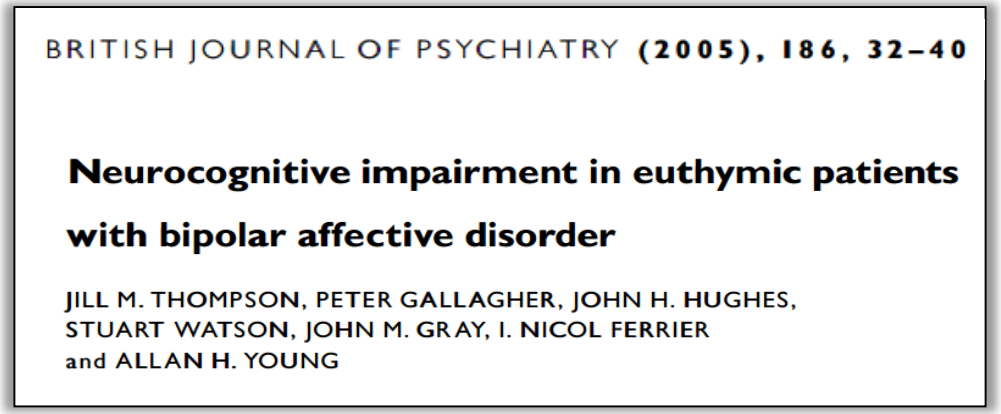
- Evidence of moderate impairment, even in first-episode, drug-free patients
- Largest effect sizes for sustained attention and executive functions.
- Poorer performance on visuo-spatial learning and memory but not verbal.

- Severity of depression (HAMD) correlated with indices from all tests of declarative learning and memory, but none of attention/executive function in patients.



Gorwood, P., et al 2008. Am. J. Psychiatry 165, 731-739.

Cognitive impairment in bipolar disorder



BRITISH JOURNAL OF PSYCHIATRY (2005), 186, 32–40

Neurocognitive impairment in euthymic patients with bipolar affective disorder

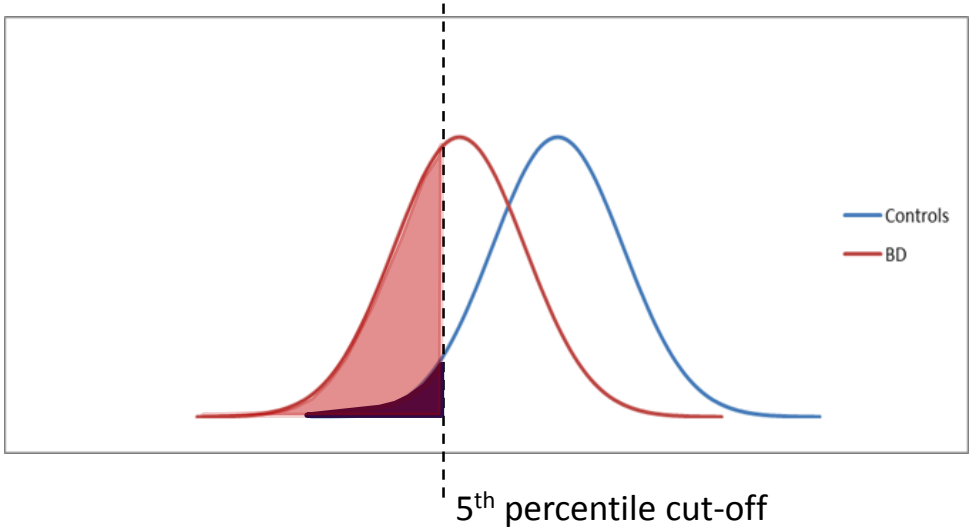
JILL M. THOMPSON, PETER GALLAGHER, JOHN H. HUGHES, STUART WATSON, JOHN M. GRAY, I. NICOL FERRIER and ALLAN H. YOUNG

- To minimise the effect of residual mood symptoms, prospective verification of mood over one month prior.

- Significantly poorer performance in BD (n=63) compared to controls (n=63) across a broad battery of tests.
- Effect sizes $0.5 < d < 0.85$ across attention/executive function, verbal and visuospatial memory and psychomotor speed

Cognitive impairment in BD euthymia

- Also explored differences in terms of effect size and proportion at a clinically impaired level (5th percentile).



Measure	Domain	≤ 5th percentile
Trail making test (A)	Psychomotor/Attention	41.9%
Digit symbol substitution	Psychomotor/Attention	35.5%
Self-ordered pointing test	Executive/WM	34.0%
Spatial working memory	Executive/WM	31.8%
Vigil CPT (omissions)	Attention	30.7%

Cognitive impairment in BD depression

Psychological Medicine (2014), **44**, 961–974. © Cambridge University Press 2013
doi:10.1017/S0033291713001487

ORIGINAL ARTICLE

Neurocognitive functioning in bipolar depression: a component structure analysis

P. Gallagher[1]*, J. M. Gray[1], S. Watson[1], A. H. Young[2] and I. N. Ferrier[1]

[1] *Institute of Neuroscience (Academic Psychiatry), Newcastle University, UK*
[2] *Centre for Mental Health, Imperial College London, UK*

- N=100 (53 depressed BD, 47 controls).

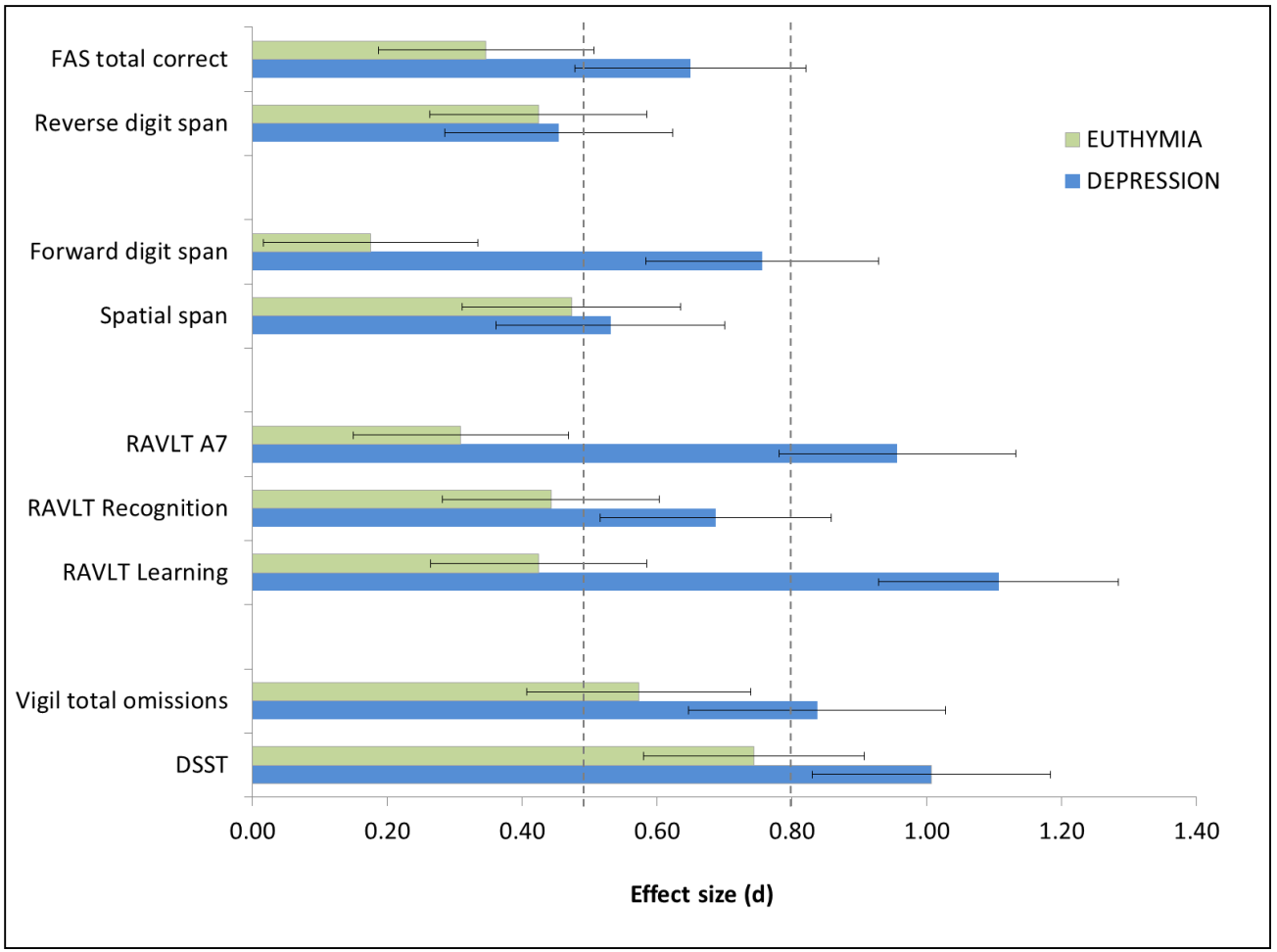
Cognitive profile - euthymia *vs.* depression

Executive/WM

Memory span

Verbal memory

Attention/ Psychomotor speed



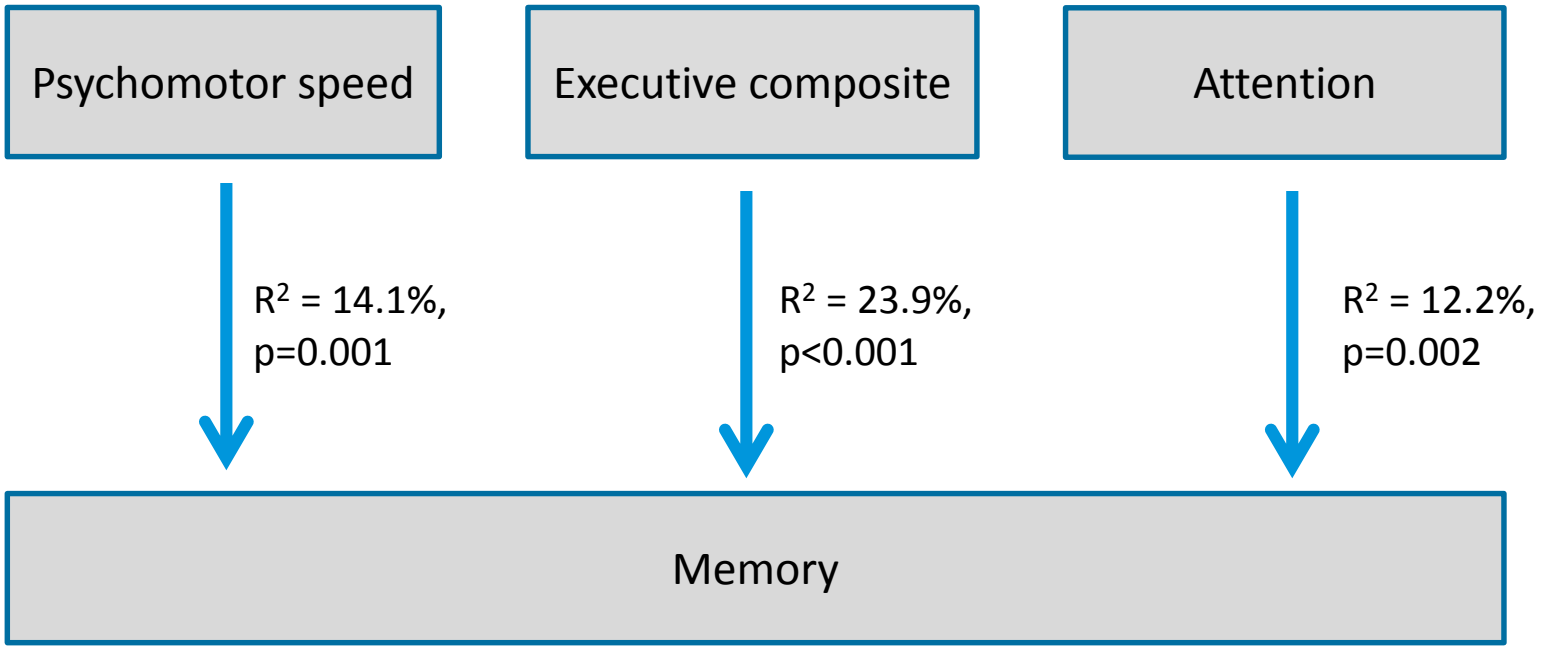
Pooled data from: - Thompson JM, Gallagher P, Hughes JH, Watson S, Gray JM, Ferrier IN, Young AH (2005). *British Journal of Psychiatry* 186, 32-40
- Gallagher P, Gray JM, Watson S, Young AH, Ferrier IN (2014). *Psychological Medicine* 44, 961–974.

Cognitive impairment in BD – work in progress

- Cognitive hierarchy – are there ‘core’ deficits?
- Is intra-individual variability important?

Cognitive hierarchy in bipolar disorder

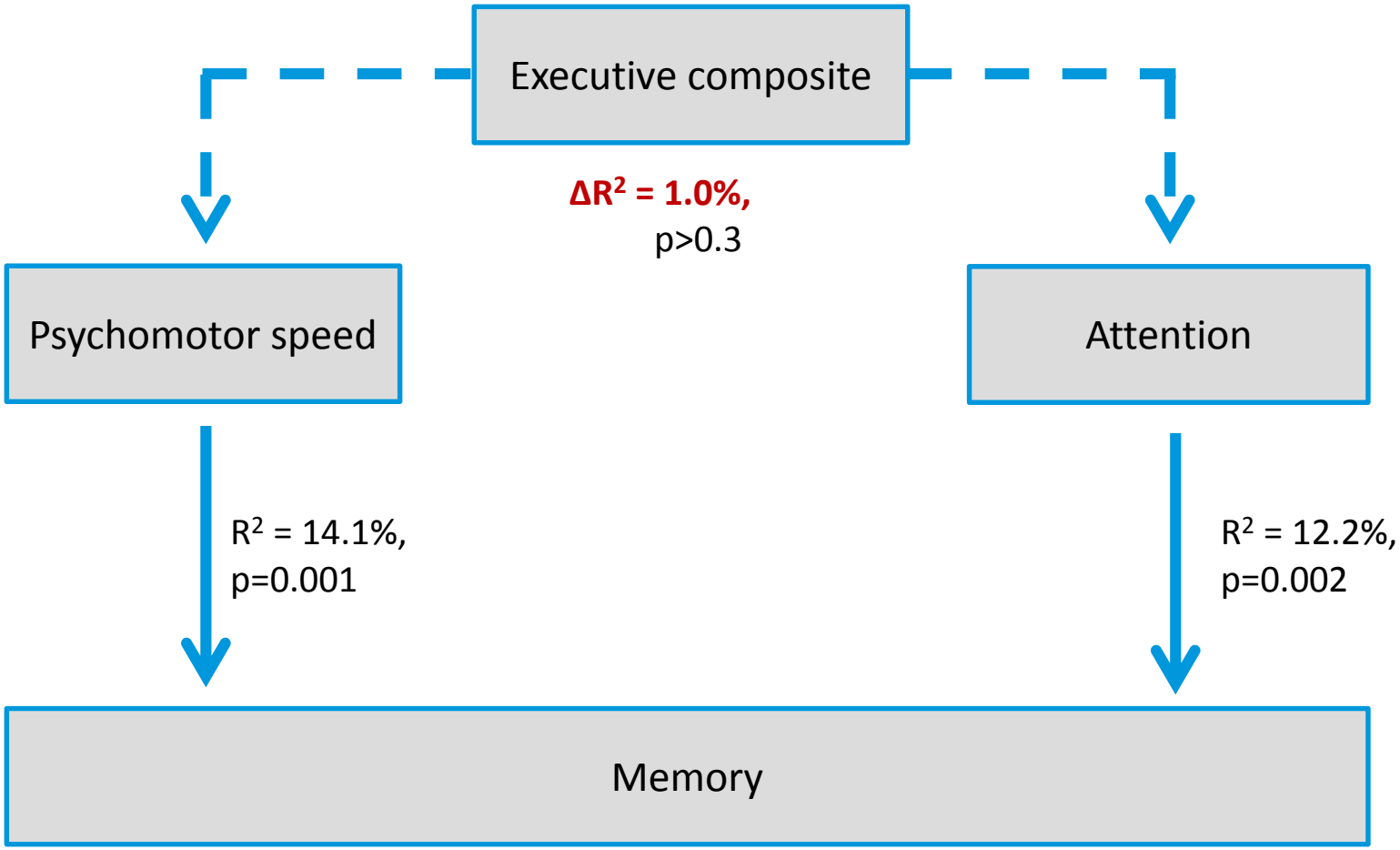
depression



n=43 bipolar depressed, n=32 controls

Cognitive hierarchy in bipolar disorder

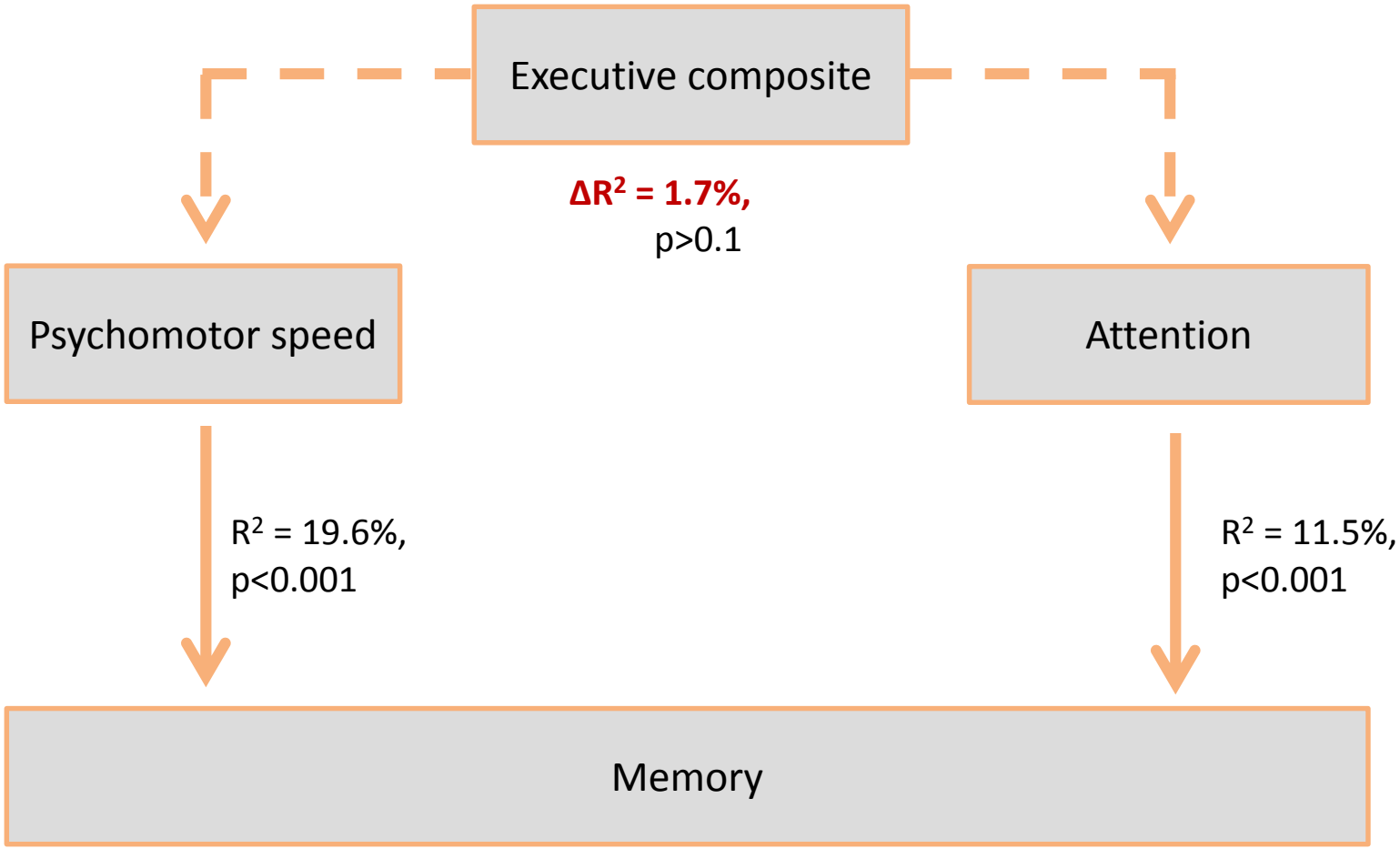
depressed



n=43 bipolar depressed, n=32 controls

Cognitive hierarchy in bipolar disorder

euthymia

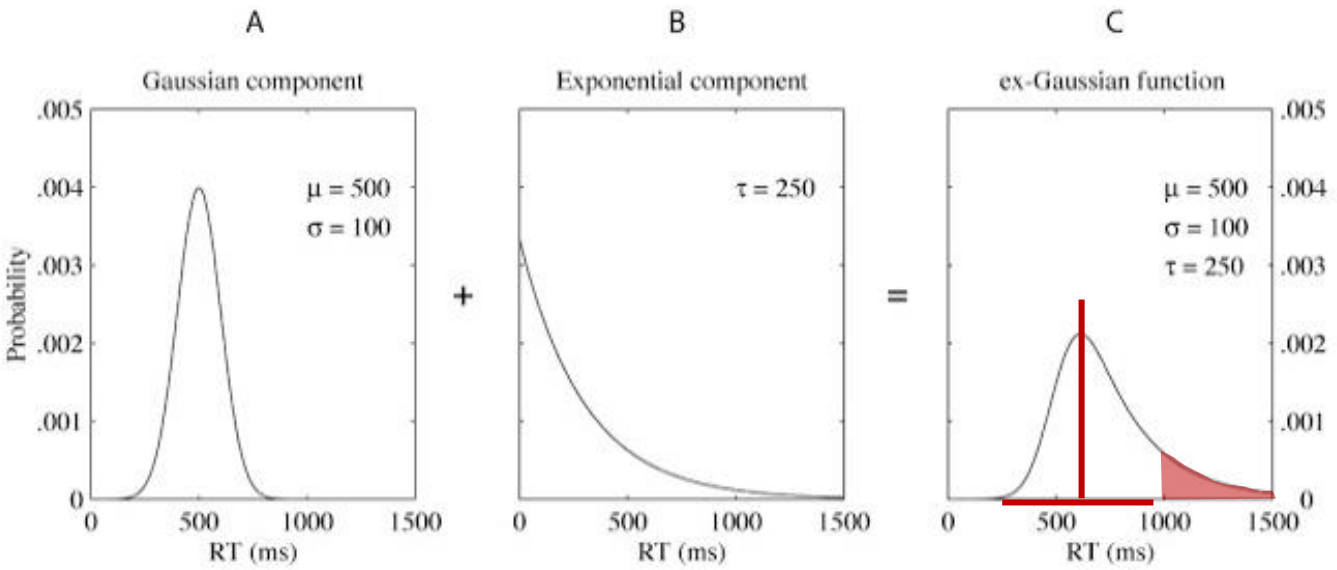


n=63 bipolar euthymic, n=62 controls

Cognitive intra-individual variability

- Does ex-Gaussian modelling improve discrimination of attentional RT measures in mood disorder?

Lacouture 2008



- Mu and sigma: mean and sd of the Gaussian (normal) component

- Tau: the 'slow tail' of the distribution

Cognitive intra-individual variability

Psychological Medicine (2015), **45**, 2985–2997. © Cambridge University Press 2015
doi:10.1017/S0033291715000926

ORIGINAL ARTICLE

Neurocognitive intra-individual variability in mood disorders: effects on attentional response time distributions

P. Gallagher[1*], J. Nilsson[1,2], A. Finkelmeyer[1], M. Goshawk[1], K. A. Macritchie[3], A. J. Lloyd[1,4], J. M. Thompson[1], R. J. Porter[5], A. H. Young[6], I. N. Ferrier[1], R. H. McAllister-Williams[1,4] and S. Watson[1,4]

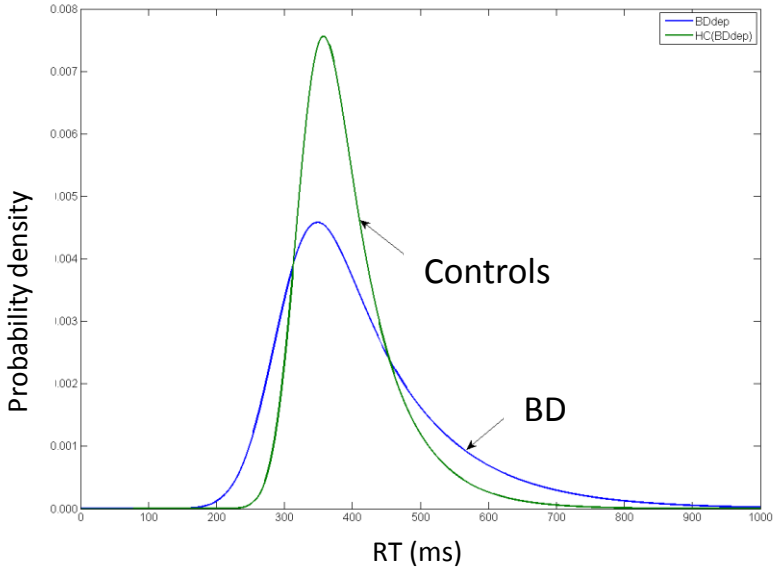
- Vigil Continuous Performance Test
  - 8 minute sustained test (requiring 100 target responses)
  - Reaction time recorded for each target response.

- 138 healthy controls and 158 patients with a mood disorder
  - 86 euthymic BD, 33 depressed BD and 39 medication-free MDD patients.

Cognitive variability – BD

depression

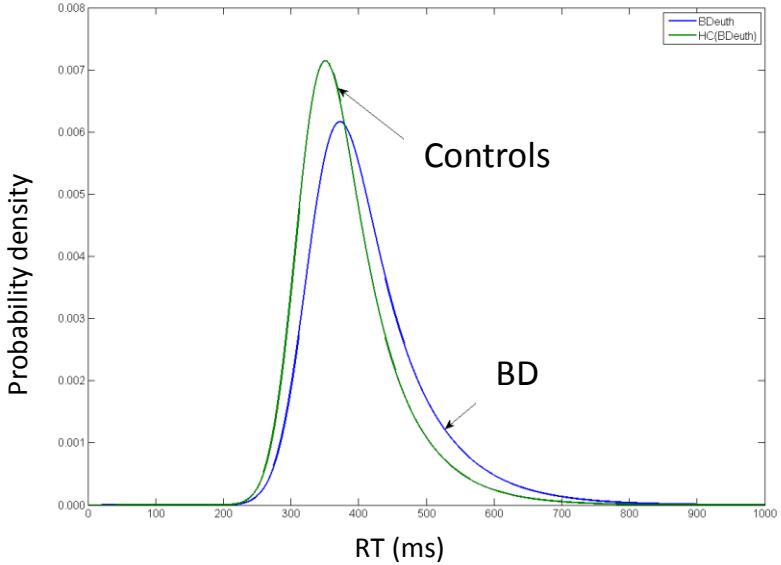
	BD depressed (n=33)		Control comparison (n=33)			
	Mean	SD	Mean	SD		
iSD	143.78	56.21	80.72	29.70	**$F_{1,64} = 32.47$**	**$p < 0.0001$**
Mu	295.98	87.66	324.63	82.76	$F_{1,64} = 1.86$	$p = 0.177$
Sigma	45.23	33.85	29.78	18.46	**$F_{1,64} = 5.29$**	**$p = 0.025$**
Tau	117.33	59.40	66.29	22.32	**$F_{1,64} = 21.35$**	**$p < 0.0001$**



d= 1.14

euthymia

	BD euthymic (n=86)		Control comparison (n=86)			
	Mean	SD	Mean	SD		
iSD	95.85	29.93	85.43	33.34	**$F_{1,170} = 4.79$**	**$p = 0.030$**
Mu	332.17	76.55	315.96	75.93	$F_{1,170} = 1.94$	$p = 0.165$
Sigma	37.68	21.19	33.15	21.78	$F_{1,170} = 1.92$	$p = 0.168$
Tau	78.85	32.55	66.77	28.98	**$F_{1,170} = 6.60$**	**$p = 0.011$**



d= 0.39

Cognitive variability – MDD

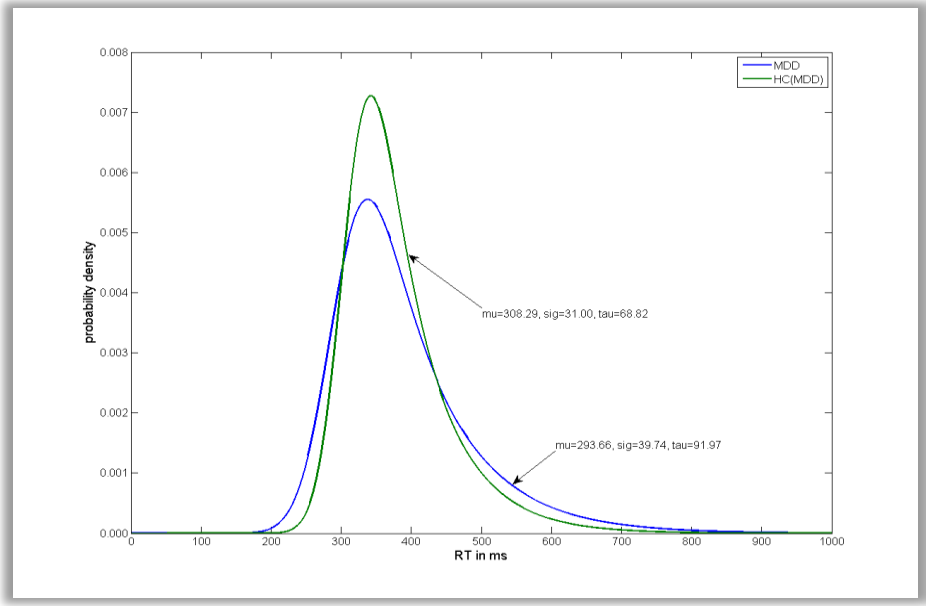
McAllister-Williams *et al. BMC Psychiatry* 2013, **13**:205
http://www.biomedcentral.com/1471-244X/13/205

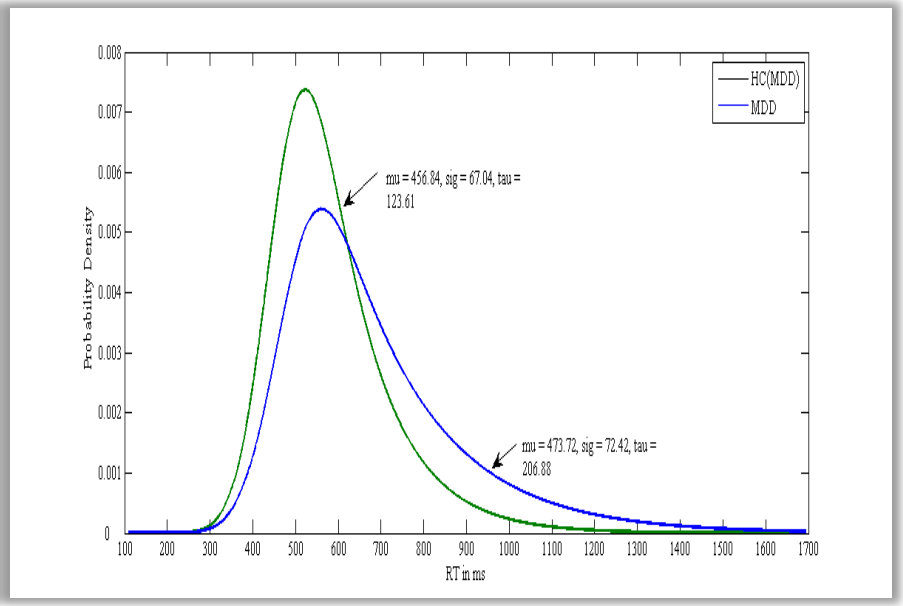
BMC Psychiatry

STUDY PROTOCOL **Open Access**

Study protocol for the randomised controlled trial: Antiglucocorticoid augmentation of anti-Depressants in Depression (The ADD Study)

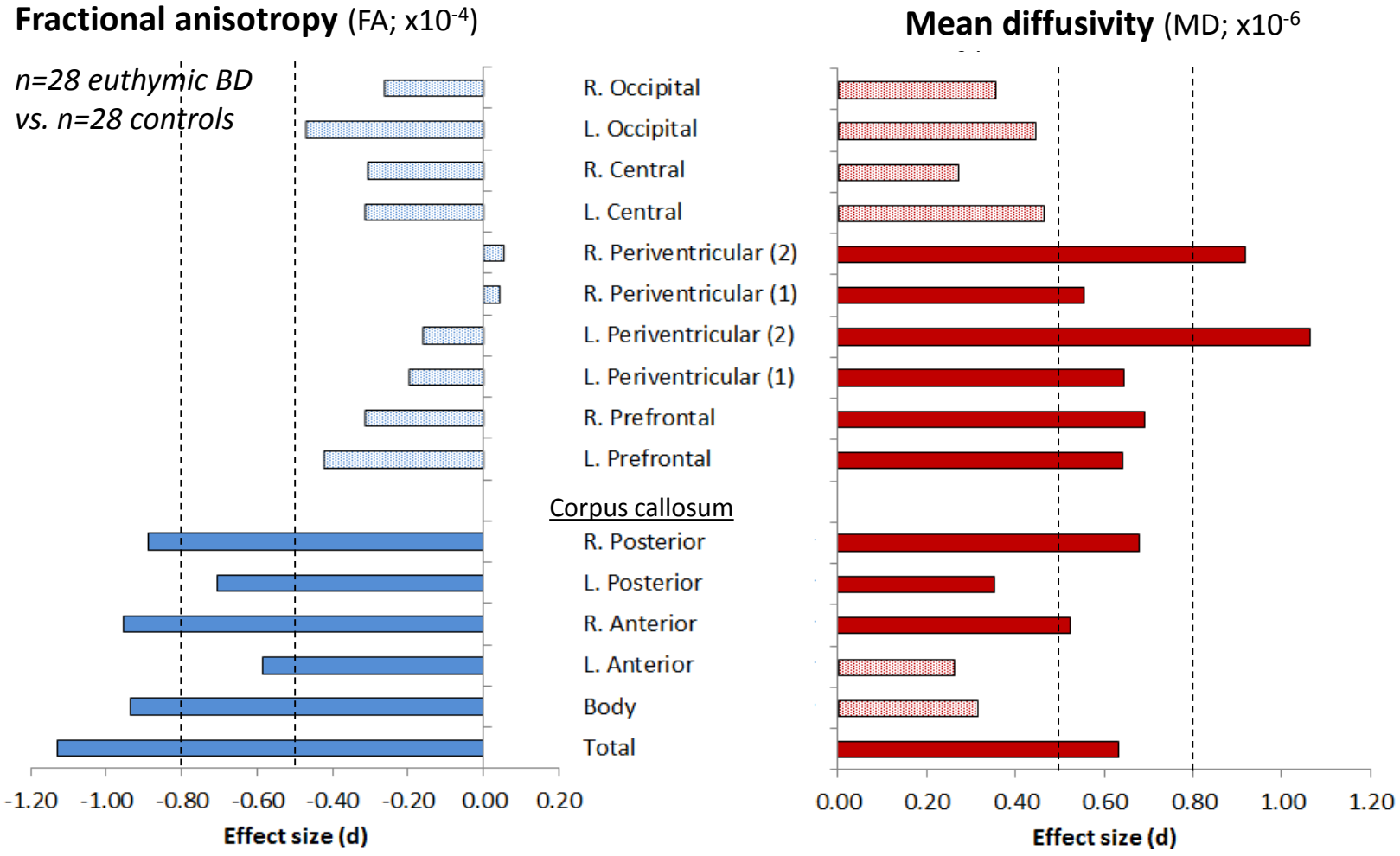
R Hamish McAllister-Williams[1,11*], Eleanor Smith[2], Ian M Anderson[3], Jane Barnes[4], Peter Gallagher[1], Heinz CR Grunze[1], Peter M Haddad[3], Allan O House[5], Tom Hughes[6], Adrian J Lloyd[1], Elaine MM McColl[4], Simon HS Pearce[7], Najma Siddiqi[8], Baxi Sinha[9], Chris Speed[4], I Nick Steen[4], June Wainright[10], Stuart Watson[1], Fiona H Winter[10] and I Nicol Ferrier[1]





What underlies these deficits?

- "WM abnormalities one of the most replicated findings in mood disorder" (Beyer 2009).



Macritchie KA, Lloyd AJ, Bastin ME, Vasudev K, Gallagher P, Eyre R, Marshall I, Wardlaw JM, Ferrier IN, Moore PB, Young AH (2010). *BJ Psych* 196, 52-58.

Future directions

Northern Centre for Mood Disorders

Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [^{11}C]PBR28 PET Brain Imaging Study

Peter S. Bloomfield, M.Sc., Sudhakar Selvaraj, M.D., Ph.D., Mattia Veronese, Ph.D., Gaia Rizzo, Ph.D., Alessandra Bertoldo, Ph.D., David R. Owen, M.D., Ph.D., Michael A.P. Bloomfield, M.D., Ilaria Bonoldi, M.D., Nicola Kalk, M.D., Federico Turkheimer, Ph.D., Philip McGuire, M.D., Ph.D., Vincenzo de Paola, Ph.D., Oliver D. Howes, M.D., Ph.D.

Carl Johan Ekman, MD; Carl Sellgren, MD, PhD; Bob Olsson, PhD; Henrik Zetter
Kaj Blennow, MD, PhD; Erik Pålsson, PhD; Mikael Landén, MD,

OPEN

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www.nature.com/tp

REVIEW

Glia and immune cell signaling in bipolar disorde
from neuropharmacology and molecular imaging
application

CC Watkins[1], A Sawa[1] and MG Pomper[1,2]

CSF neuroinflammatory biomarkers in bipolar disorder are associated with cognitive impairment

Sindre Rolstad[a,*], Joel Jakobsson[a], Carl Sellgren[b], Anniella Isgren[a], Carl Johan Ekman[c], Maria Bjerke[a], Kaj Bl
Henrik Zetterberg[a,d], Erik Pålsson[a], Mikael Landén[a,b]

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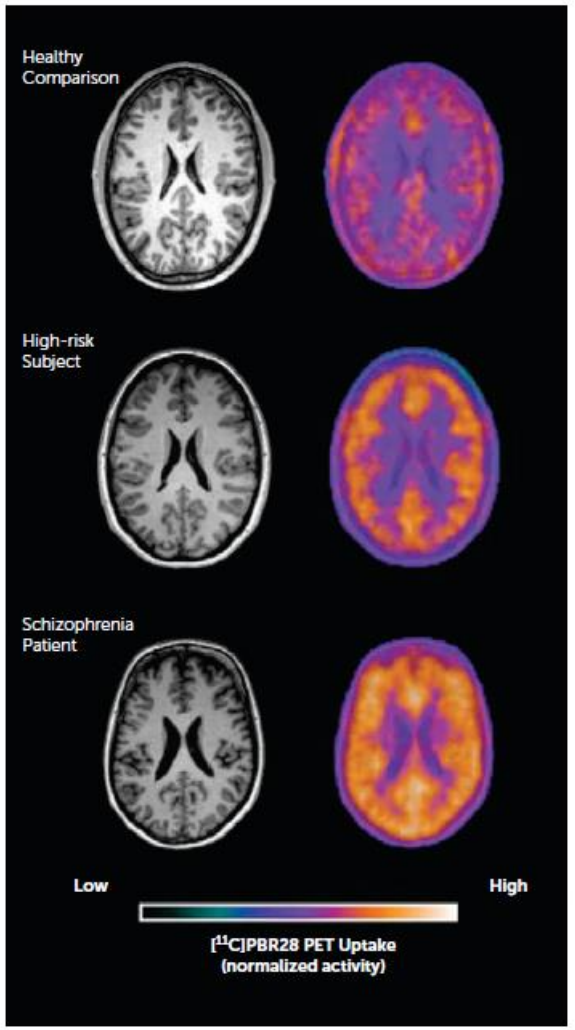

Some lessons from the past …

Northern Centre for Mood Disorders

Sectional page 5

Proceedings of the Royal Society of Medicine

Vol. 45
445

[*February* 12, 1952]

DISCUSSION ON THE ROLE OF THE PSYCHOLOGIST IN PSYCHIATRIC PRACTICE

It would seem evident that, if integrative research is to develop, a framework of psychological knowledge common to both psychiatrists and psychologists should be created as its essential condition. Professor Aubrey Lewis (1950) has written that: " . . . in the main, the future (of psychiatry) must be determined by progress in our knowledge of physiology and biochemistry, sociology, genetics and, most of all, psychology."

Full co-operation in research must develop from common thinking and discussion and this, in its turn, demands a background of appropriate instruction in the Universities and Medical Schools. Such instruction must affect both psychiatrists and psychologists and should set the stage for mutual comprehension in methodology, clinical practice and research. Only in some such way as this can we hope to overcome the difficulties which at present keep us apart and come to understand one another's point of view.

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Prof. Allan Young

Christchurch, NZ
Prof. Richard Porter

Nijmegen Institute for Cognition and Information, The Netherlands
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