Northumberland Tyne and Wear NHS Foundation Trust

Northern Centre for Mood Disorders

Newcastle University Institute of Neuroscience

PAX, magnets and mushrooms

R. Hamish McAllister-Williams,

Professor of Affective Disorders

Academic Lead, NCMD

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NCMD Aims

- To provide more hope to more people with mood disorders through an improvement of clinical care for patients brought about by research and education
- To be an international centre of excellence in research into mood disorders

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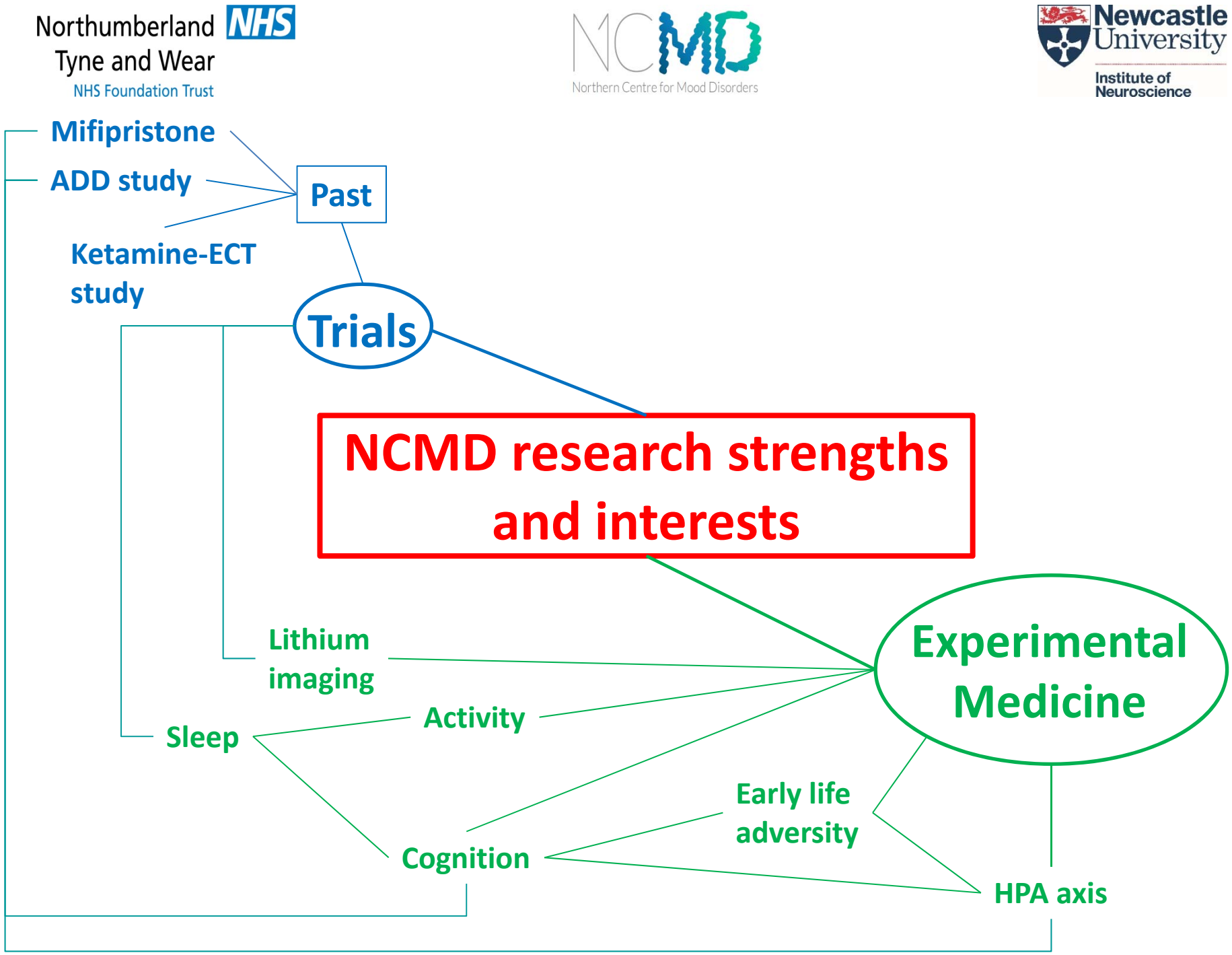
Research

- To achieve our research goals NCMD will:
  - Build on a major Northern England strength – population stability
  - Focus research on areas where the North of England has an international reputation and local strengths
  - Support the development of research strengths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Mifipristone
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Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in dep… ran…

Ian M A…
Katheri…
Stephe…

Summ…
Backg…
Prelim…
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Methods In this multice… …ent care
settings in seven Natio… …atients,
who were diagnosed as… …SM-IV
criteria, aged at least 18 … …Patients
were randomly assigne… …etic for
the duration of their E… …atment
allocation, although ana… …tcome,
Hopkins Verbal Learnin… …aussian

	Ketamine group		Saline group		Repeated measures analysis	
	Mean score (SD)	n	Mean score (SD)	n	Difference ketamine–saline adjusted for baseline (95% CI)	p value
HVLT-R						
Delayed recall						
Baseline	6·12 (2·69)	33	5·86 (3·63)	37	..	..
Mid-ECT*	5·17 (2·92)	29	5·54 (3·42)	35	−0·43 (−1·73 to 0·87)	0·51
End of treatment	5·69 (2·80)	26	5·44 (3·18)	32	−0·04 (−1·22 to 1·13)	0·94
1-month follow-up	6·70 (2·67)	23	7·26 (2·63)	23	−0·53 (−1·66 to 0·60)	0·36
4-month follow-up	6·63 (3·17)	19	8·11 (2·83)	18	−1·40 (−2·91 to 0·12)	0·07

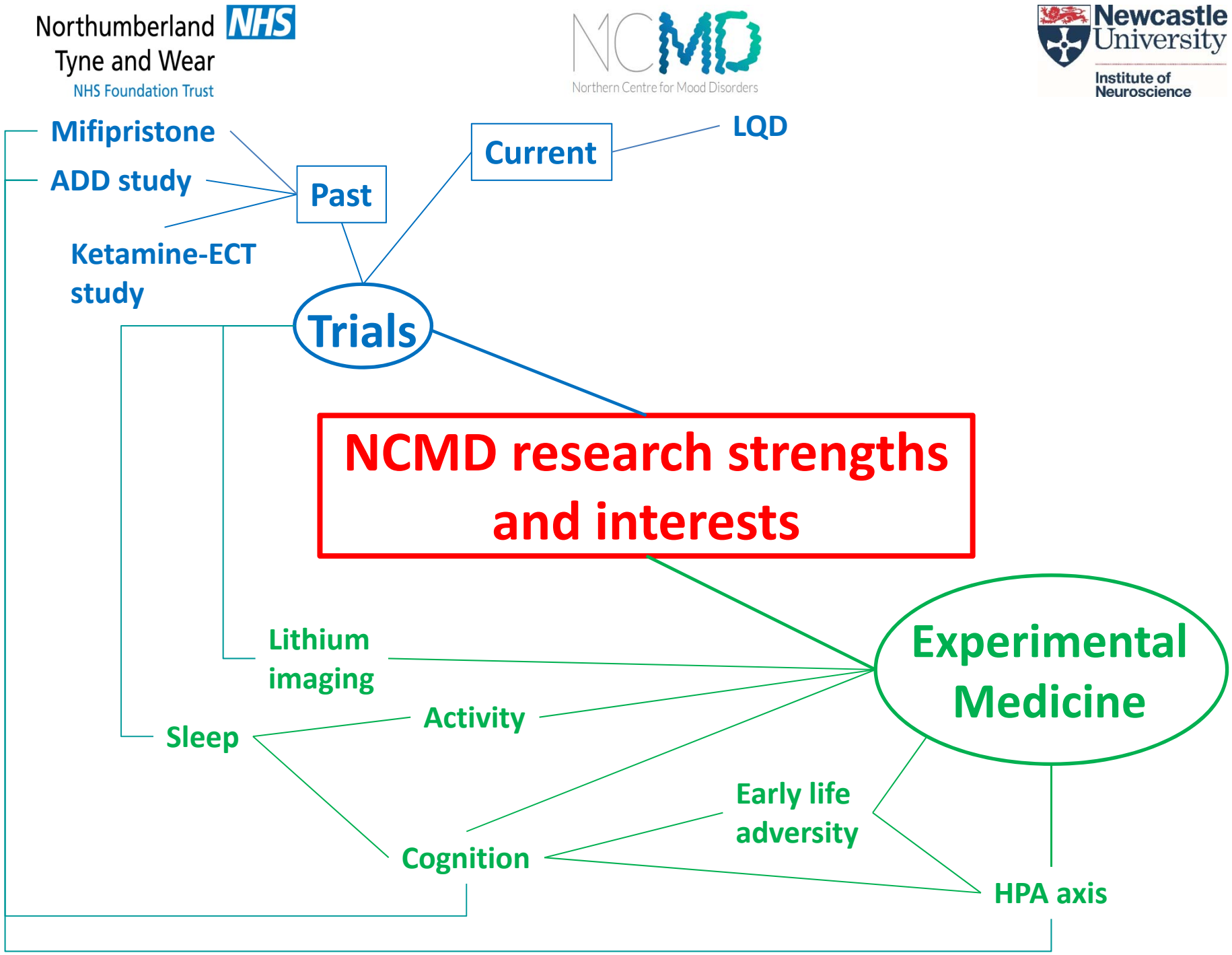
	Ketamine group		Saline group		Treatment effect	
	Mean score (SD)	n	Mean score (SD)	n	Estimated difference in slopes (95% CI)	p value
MADRS						
Baseline	31·8 (7·4)	33	35·2 (8·4)	37	..	..
Mid-ECT*	25·4 (9·8)	31	25·9 (12·4)	33	..	..
End of treatment	17·2 (11·6)	27	15·0 (10·4)	32	..	..
Ketamine *vs* saline from baseline up to end of treatment	..	..	..	..	−0·44 (−1·91 to 1·03)	0·56
1-month follow-up	16·8 (13·6)	24	14·8 (11·4)	23	..	..
4-month follow-up	18·0 (13·3)	19	13·5 (13·9)	18	..	..

March 27, 2017
http://dx.doi.org/10.1016/S2215-0366(17)30077-9

See Comment page 348

*Study team members are listed in the appendix

Neuroscience and Psychiatry Unit, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK (Prof I M Anderson MD,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LQD

Lithium vs. Quetiapine in Depression

A 12 month, phase IV, multi-centre, **pragmatic**, open-label trial of the clinical and cost-effectiveness of lithium versus quetiapine add-on treatment to antidepressant medication.

Chief Investigator
Professor Anthony Cleare

LQD sites

- London
- Oxford
- North East England

Principal Investigator SLaM
Professor Allan Young

Principal Investigator OHNT
Professor John Geddes

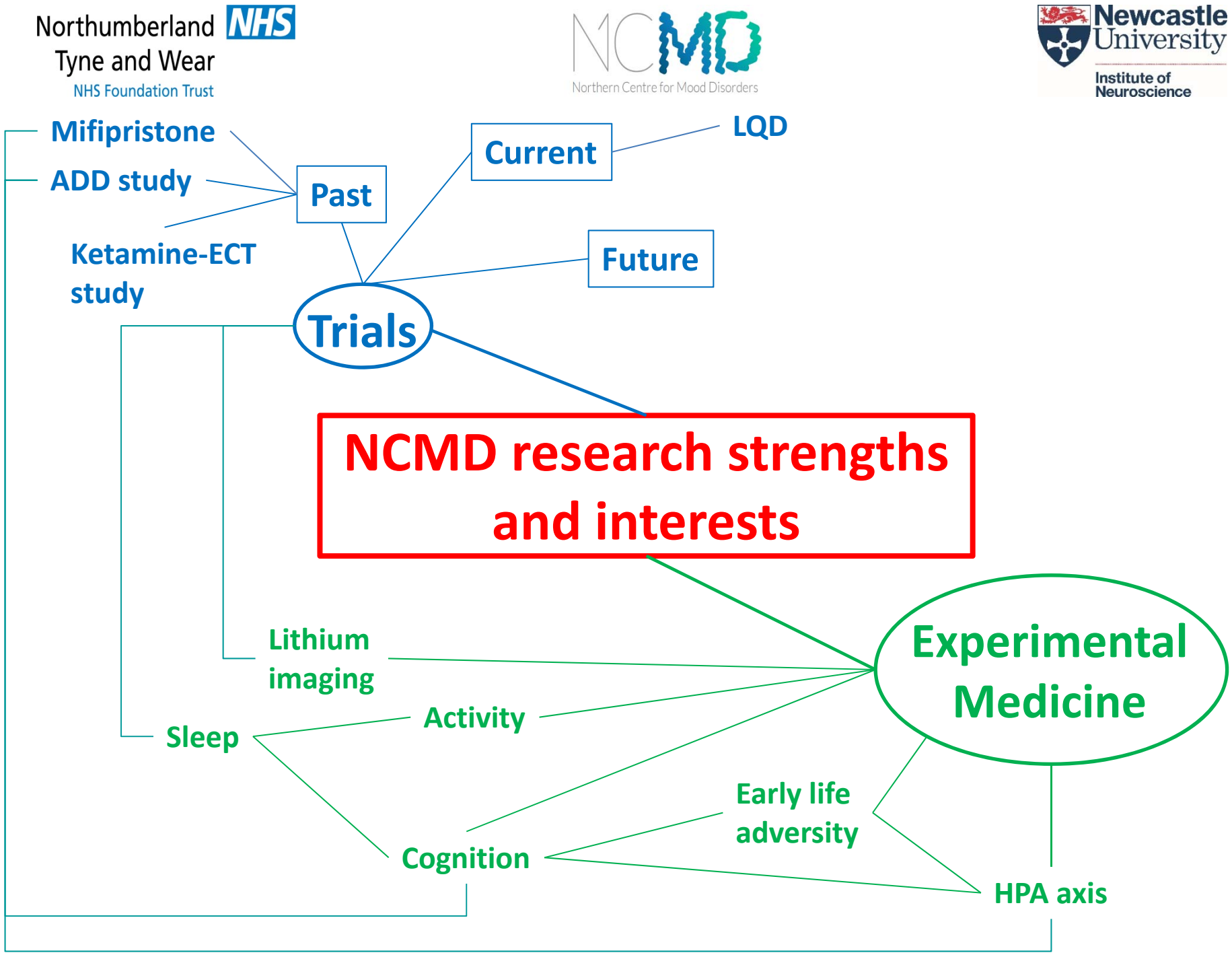
Principal Investigator NTW
Prof Hamish McAllister-Williams

Inclusion Criteria (abbreviated):

- ✓ Diagnosis of major depression
- ✓ Not responded to (or relapsed whilst taking) ≥2 antidepressants in the current episode
- ✓ On current antidepressant ≥ 6 weeks
- ✓ Aged 18 or over

Exclusion Criteria:

- X Bipolar disorder
- X Current psychosis
- X Pregnant or lactating
- X Use of lithium or quetiapine during the current episode
- X Known contraindication to either quetiapine or lithium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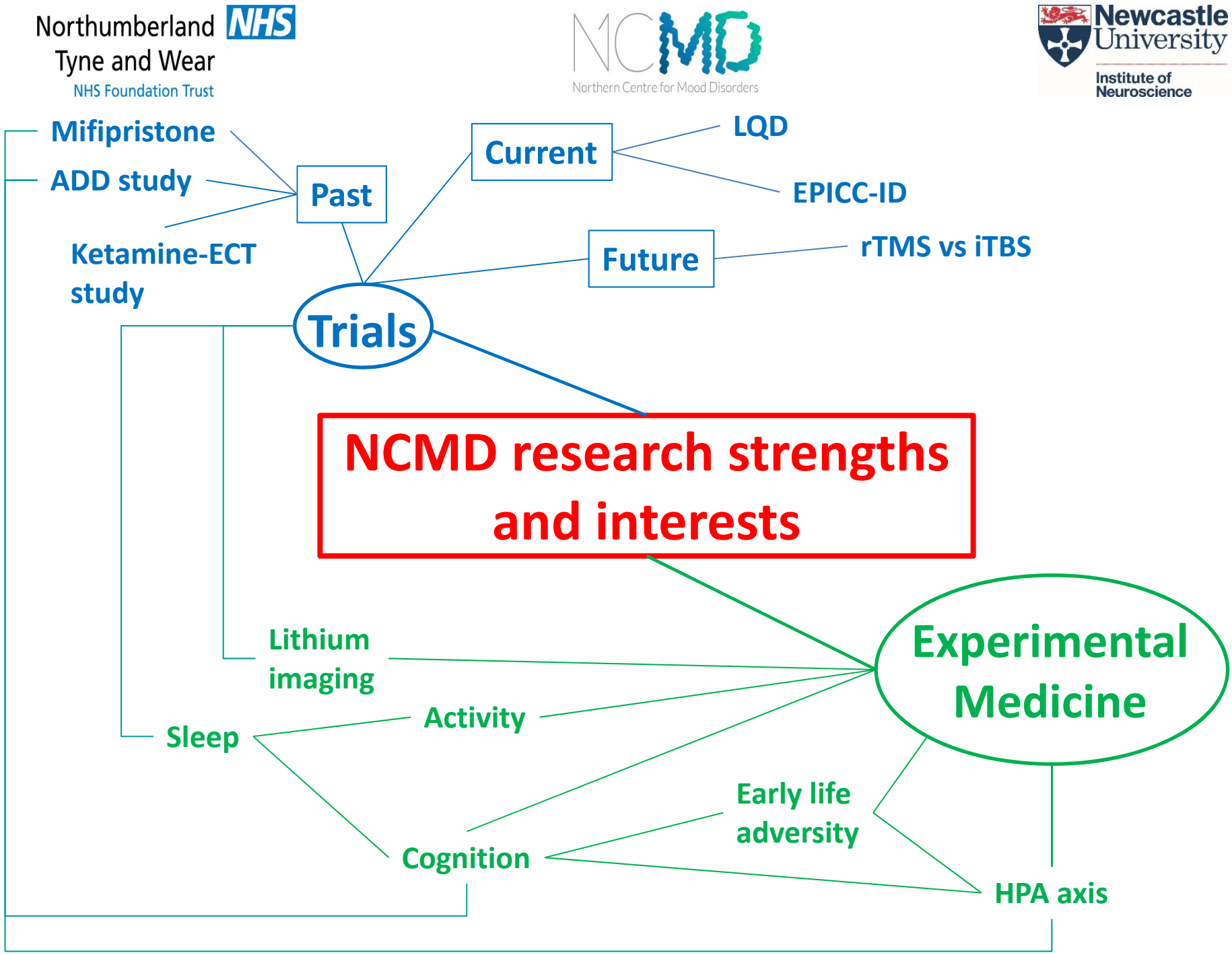
Research

- What are some of the big questions for the treatment of mood disorders?
  - How do we manage patients who are intolerant of medication
  - How do we manage patients who are non-response to medication
    - Especially those with bipolar disorder where options are limited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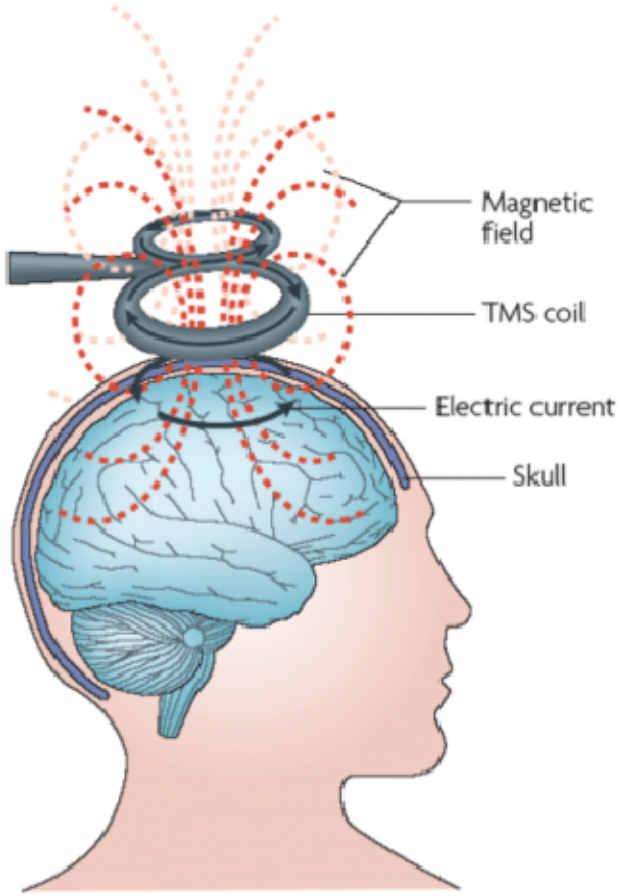
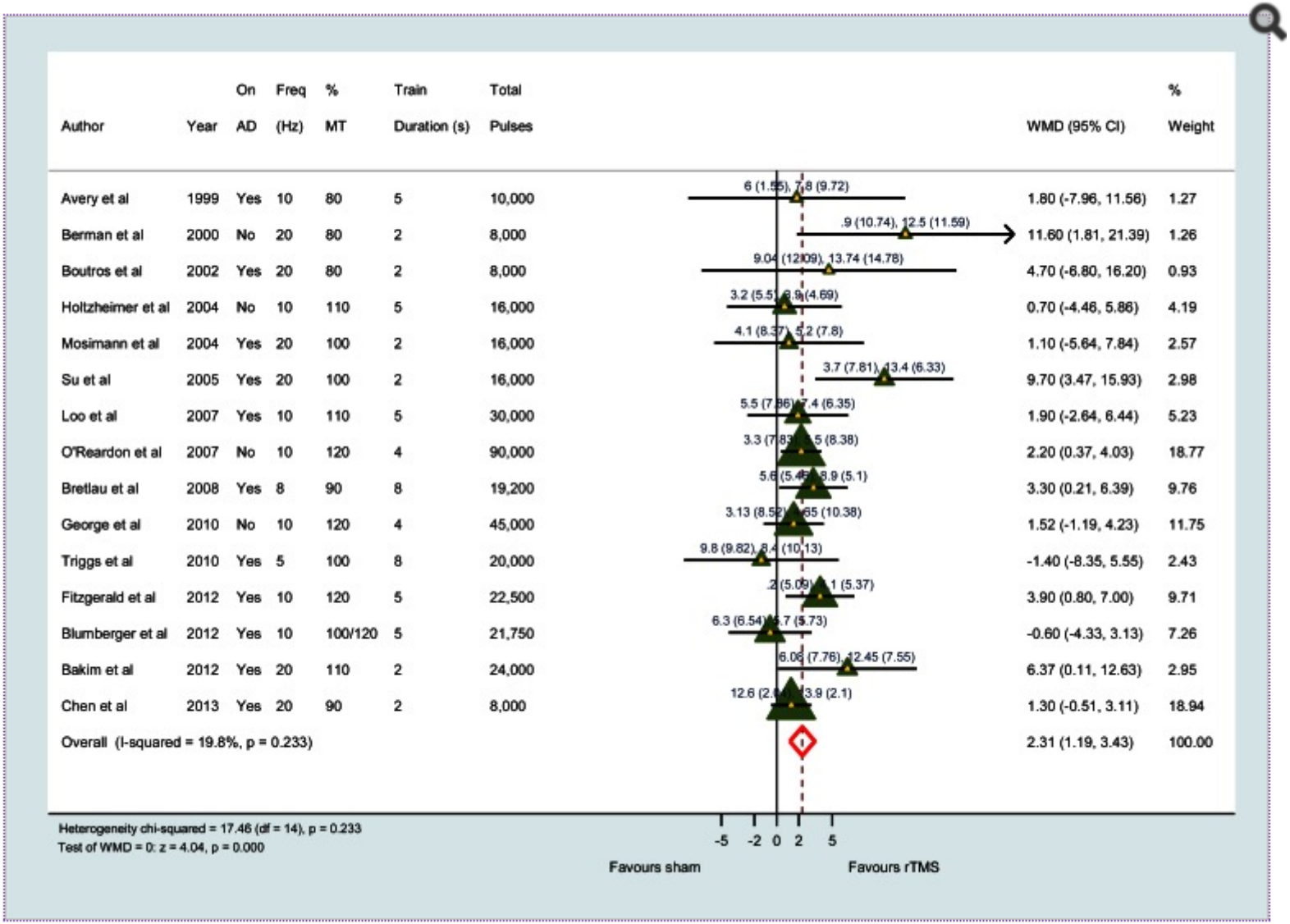
Magnets: Transcranial magnetic stimulation (TMS)

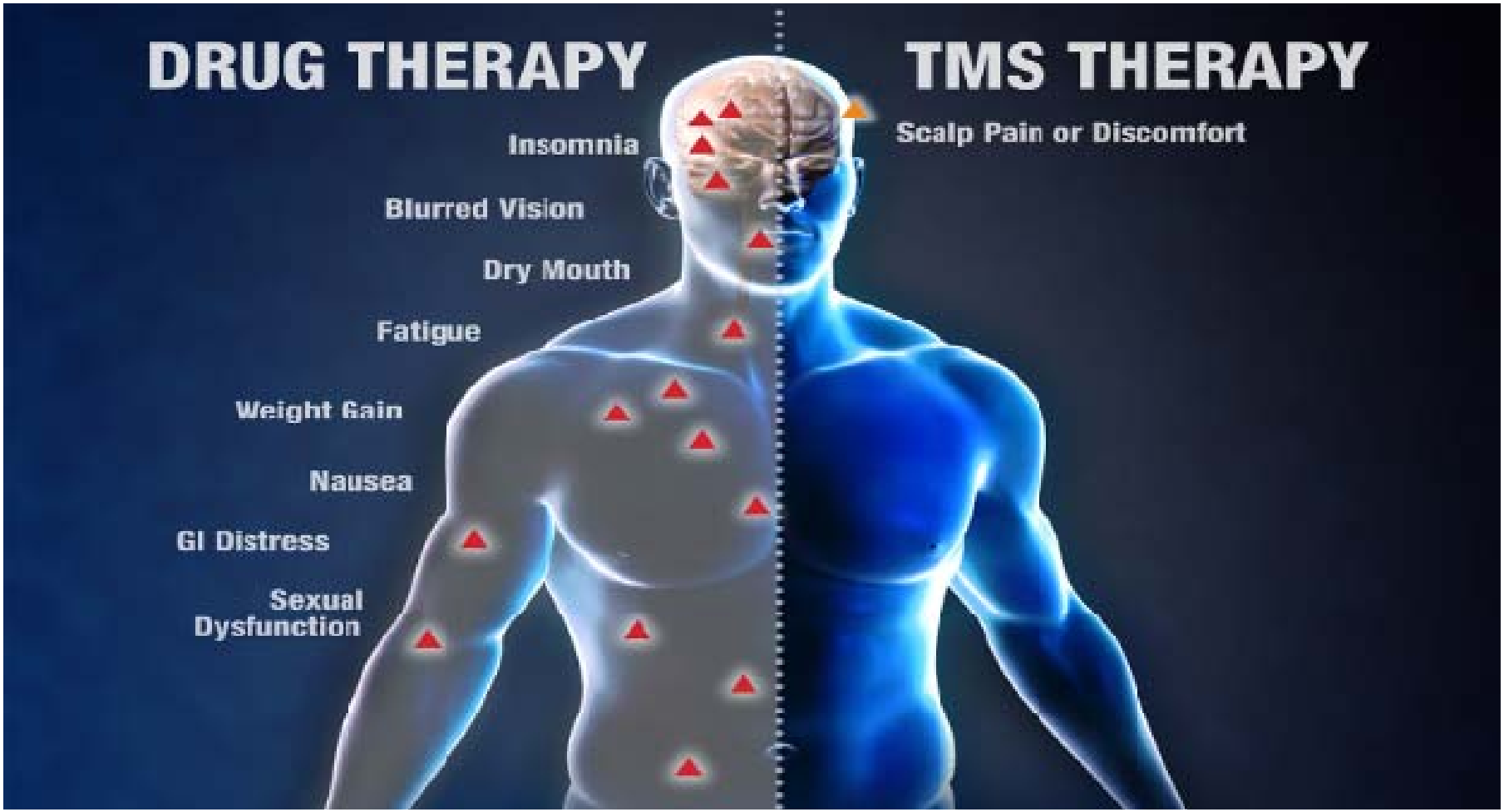


Meta-analysis of rTMS (left high frequency) vs sham in MDD



Ont Health Technol Assess Ser. 2016; 16(5): 1–66

rTMS – tolerability vs medication



NB seizures – risk very low if follow FDA guidance on stimulus parameters

iTBS vs sham

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Active TBS	Sham TBS	Relative weight
Duprat et al, 2016	0.473	0.292	0.085	-0.099	1.044	1.621	0.105	22	25	18.01
Chistyakov et al, 2015	0.654	0.371	0.138	-0.074	1.382	1.762	0.078	15	14	16.68
Prasser et al, 2015	0.410	0.322	0.103	-0.220	1.040	1.275	0.202	20	18	17.52
Li et al, 2015_unilat	0.386	0.313	0.098	-0.229	1.000	1.231	0.218	30	15	17.66
Li et al, 2015_bilat	1.616	0.412	0.170	0.809	2.424	3.923	0.000	15	15	15.97
Plewnia et al, 2014	3.058	0.515	0.265	2.049	4.066	5.941	0.000	16	16	14.16
	1.025	0.345	0.119	0.349	1.702	2.970	0.003	118	103	

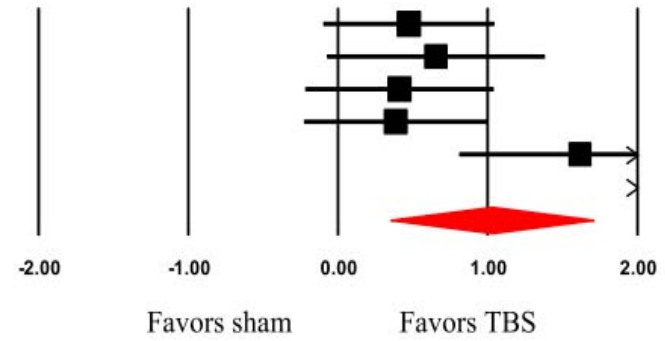


Fig. 2. Meta-analysis of Active vs. Sham TBS for MD: pre-post HAM-D scores.

Berlim et al. 2017 Journal of Psychiatric Research 90:102-109

- 80% of responders still responders at 14 weeks (Li CT et al. Brain 137:2088-2098)
- NIHR EME funded RCT of standard left rTMS vs image guided iTBS, led from Nottingham (Richard Morriss) with centres in Northampton, London and Newcastle

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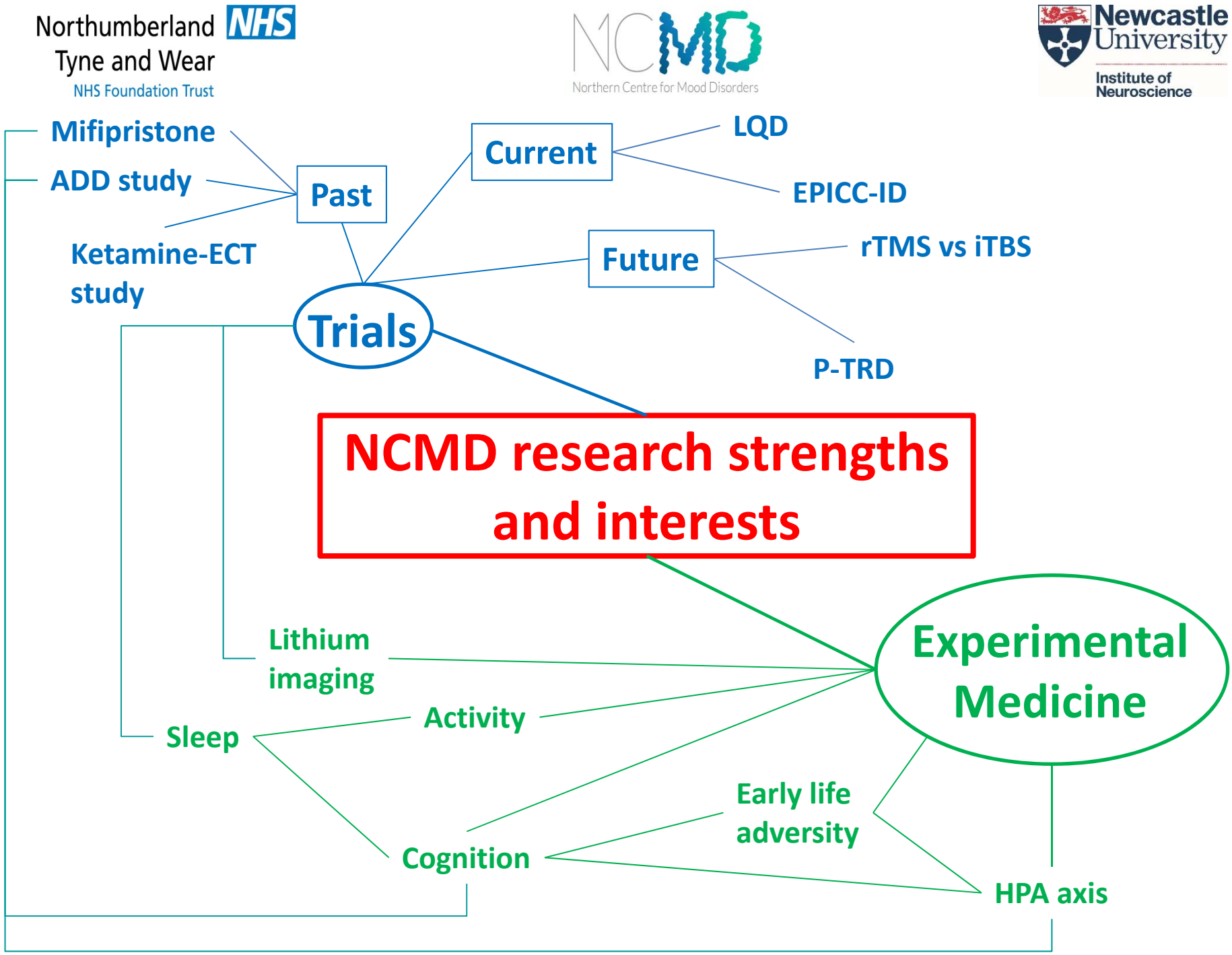
Randomised double-blind controlled trial of connectivity guided theta burst transcranial magnetic stimulation versus repetitive transcranial magnetic stimulation for treatment resistant moderate to severe depression: evaluation of efficacy, cost effectiveness and mechanism of action

- NIHR EME funded RCT of standard left sided rTMS vs image guided iTBS, led from Nottingham (Richard Morriss) with centres in Northampton, London and Newcastle
- Based on data that image guided TBS may be more effect, and with longer lasting effects, compared with standard rTMS
- For patients with **unipolar depression** who have **failed (or not tolerated) 2+ antidepressants.**
- Aim to recruit 90 odd patients over 2.5 years with recruitment **starting in Sept/Oct**
- NB TMS will be available as a clinical service within RADS by late spring/early summer.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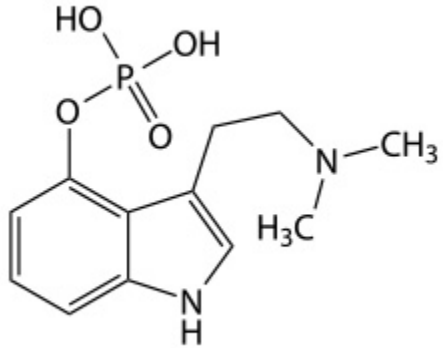
Mushrooms (magic)

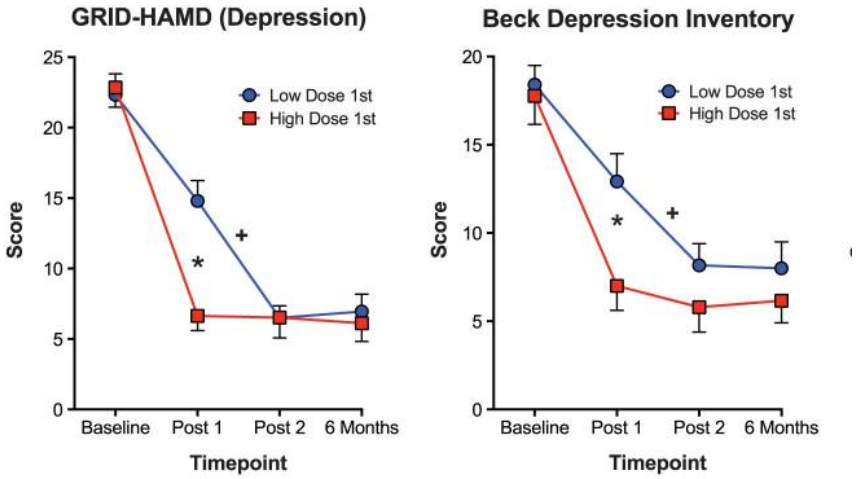


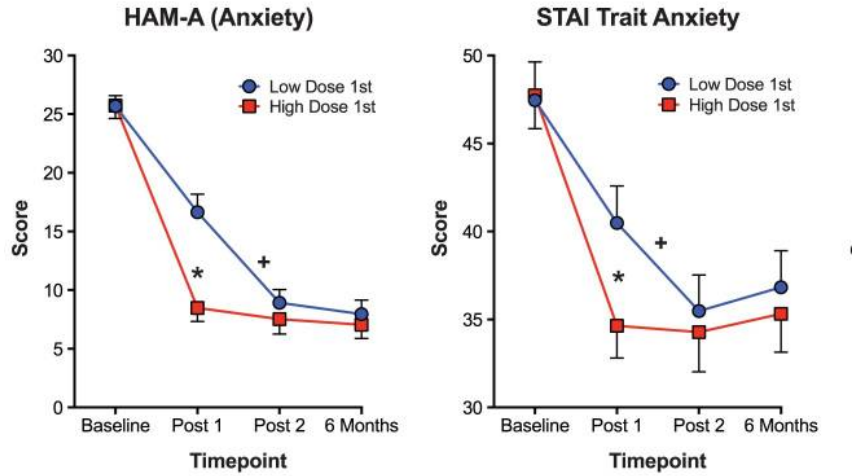
Psilocybin

- Many mushrooms are considered “magic”:
- Biological genera include *Copelandia, Gymnopilus, Inocybe, Mycena, P anaeolus, Pholiotina, Pluteus,* and *Psilocybe*.
- There are over 100 species in the genus *Psilocybe*.

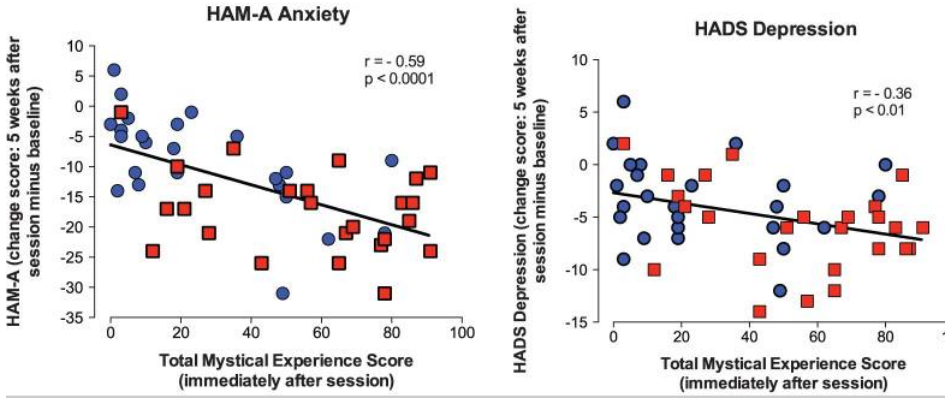
- Archaeological evidence suggests that psilocybin-containing mushrooms have been used by humans since prehistoric times.

Psilocybin for depression and anxiety in cancer patients





- 51 cancer patients with life-threatening illness and depression
- Randomised to low or high dose psilocybin in a cross over design (5 week washout)
- 6 month follow up



Griffiths et al. 2016 J Psychopharmacol 30(12) 1181-1197

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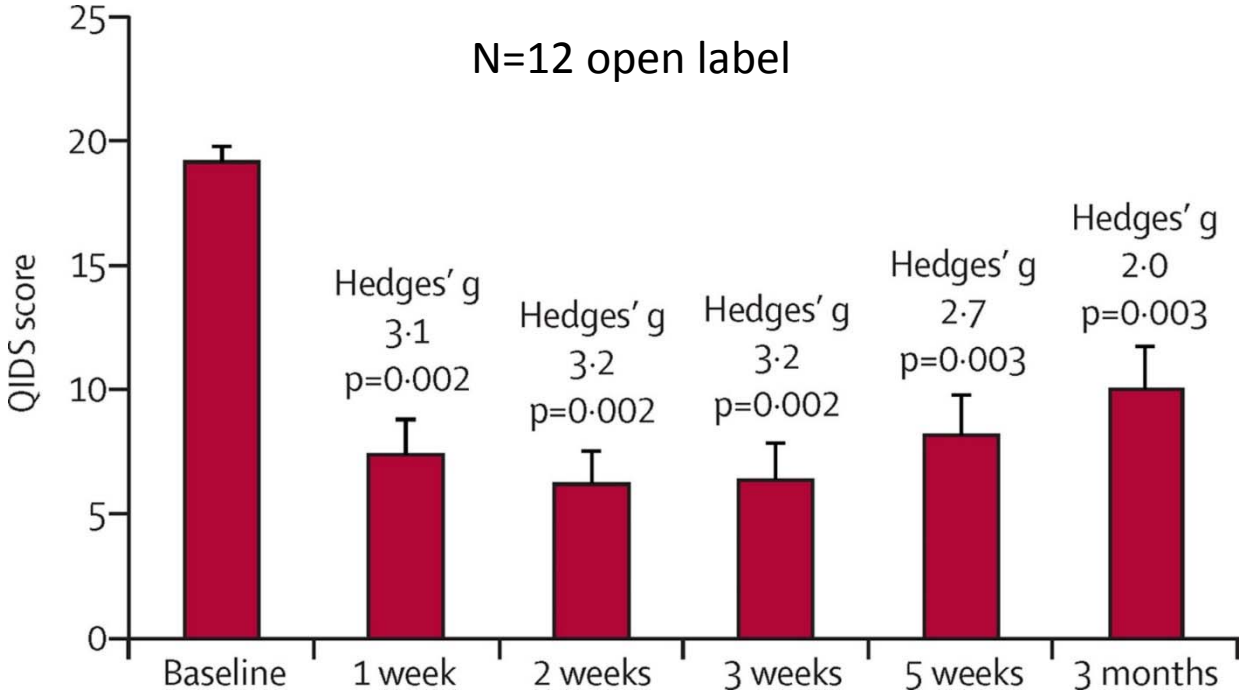
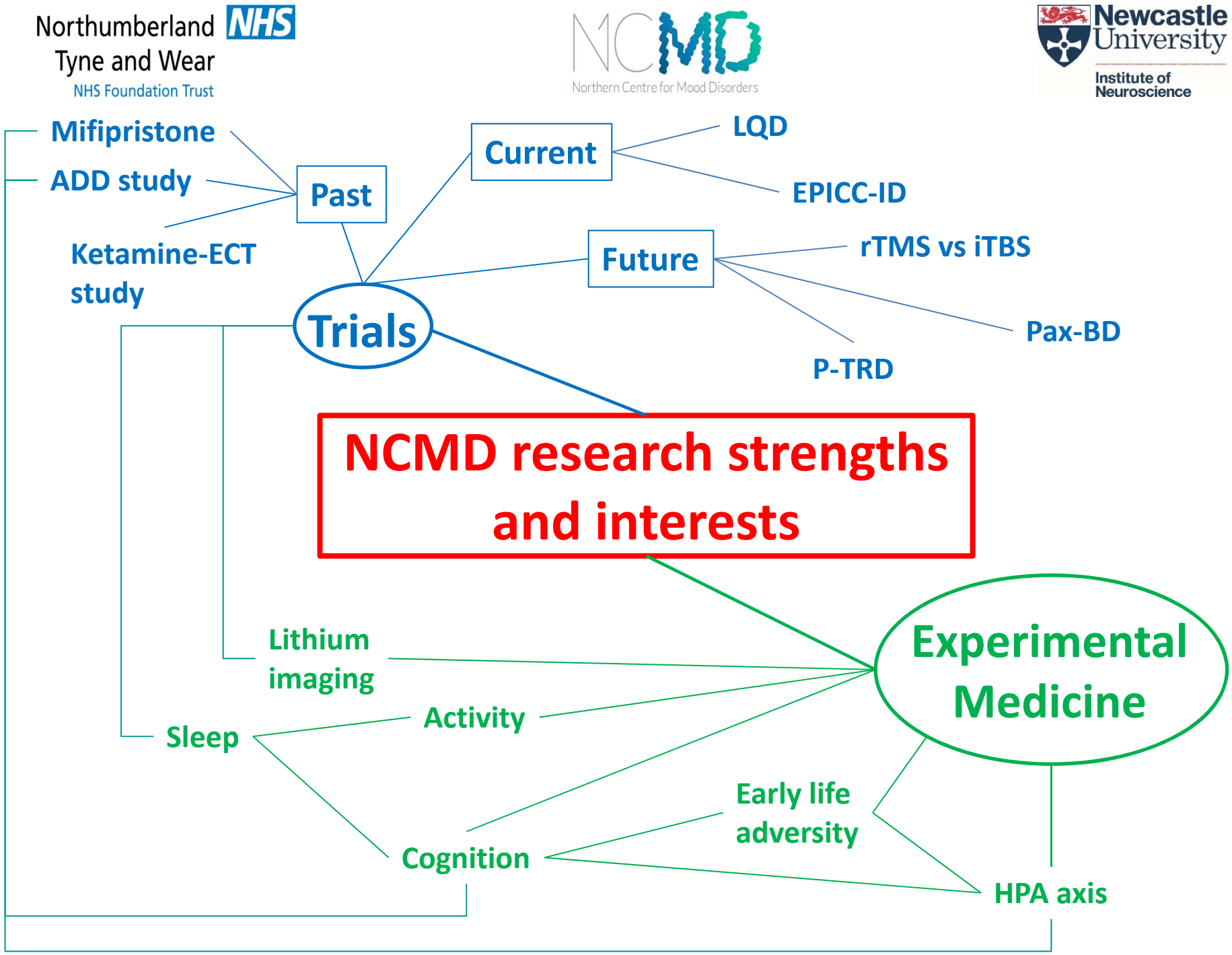
Single dose psilocybin for TRD



Carhart-Harris et al. Lancet Psychiatry. 2016 Jul;3(7):619-27

The safety and efficacy of psilocybin in participants with treatment-resistant depression (P-TRD)

- Industry funded multi-national study
- For patients with **unipolar depression** who have **failed 2 plus antidepressants** (and ideally without a history of psilocybin or hallucinogen use)
- Randomised to low or high single dose psilocybin while in a pleasant, quite and safe space with 2 “facilitators”
- Aim to recruit 30-50 patients over 2 years at the Newcastle site.
- Recruitment due to **start around April/May**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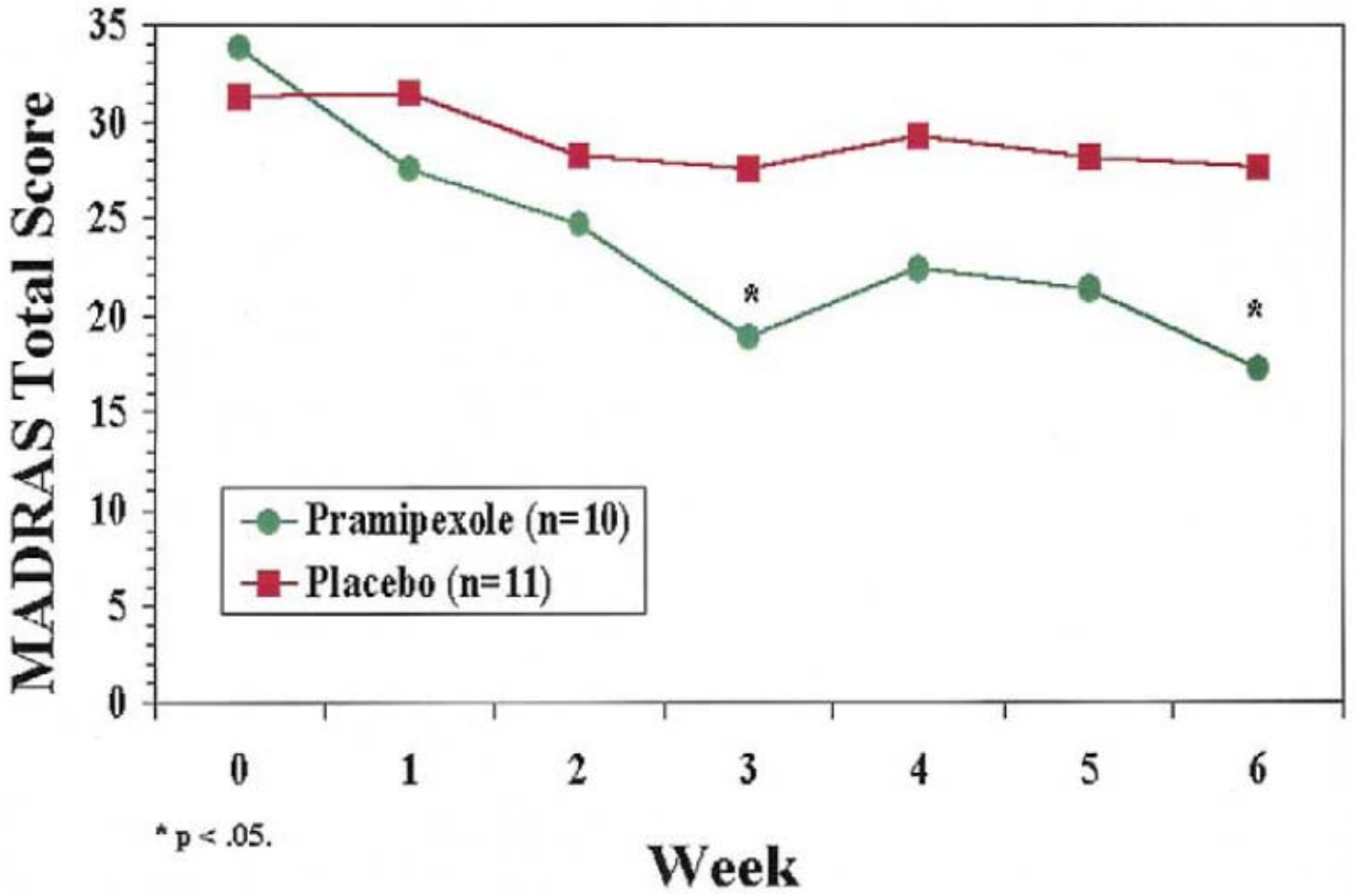
Acute depression: BAP guidelines

- If not already on long-term treatment
  - Consider quetiapine, lurasidone or olanzapine
  - There is great uncertainty about antidepressants:
    - only olanzapine/fluoxetine in combination has support as a specific treatment
    - if antidepressants are used, they should be co-prescribed with a drug for mania
  - Consider lamotrigine (incremental dosing) usually as an addition to agents preventing recurrence of mania
  - Consider ECT
  - Lithium may be considered in less severe cases (limited evidence but prelude to long-term treatment)

Acute depression: BAP guidelines

- Treatment resistant bipolar depression
  - Little trial evidence to support options:
    - ECT can be considered
    - Augmentation can be extrapolated from unipolar depression but not before evidence based bipolar disorder options exhausted.
    - Anti-manic cover will be necessary

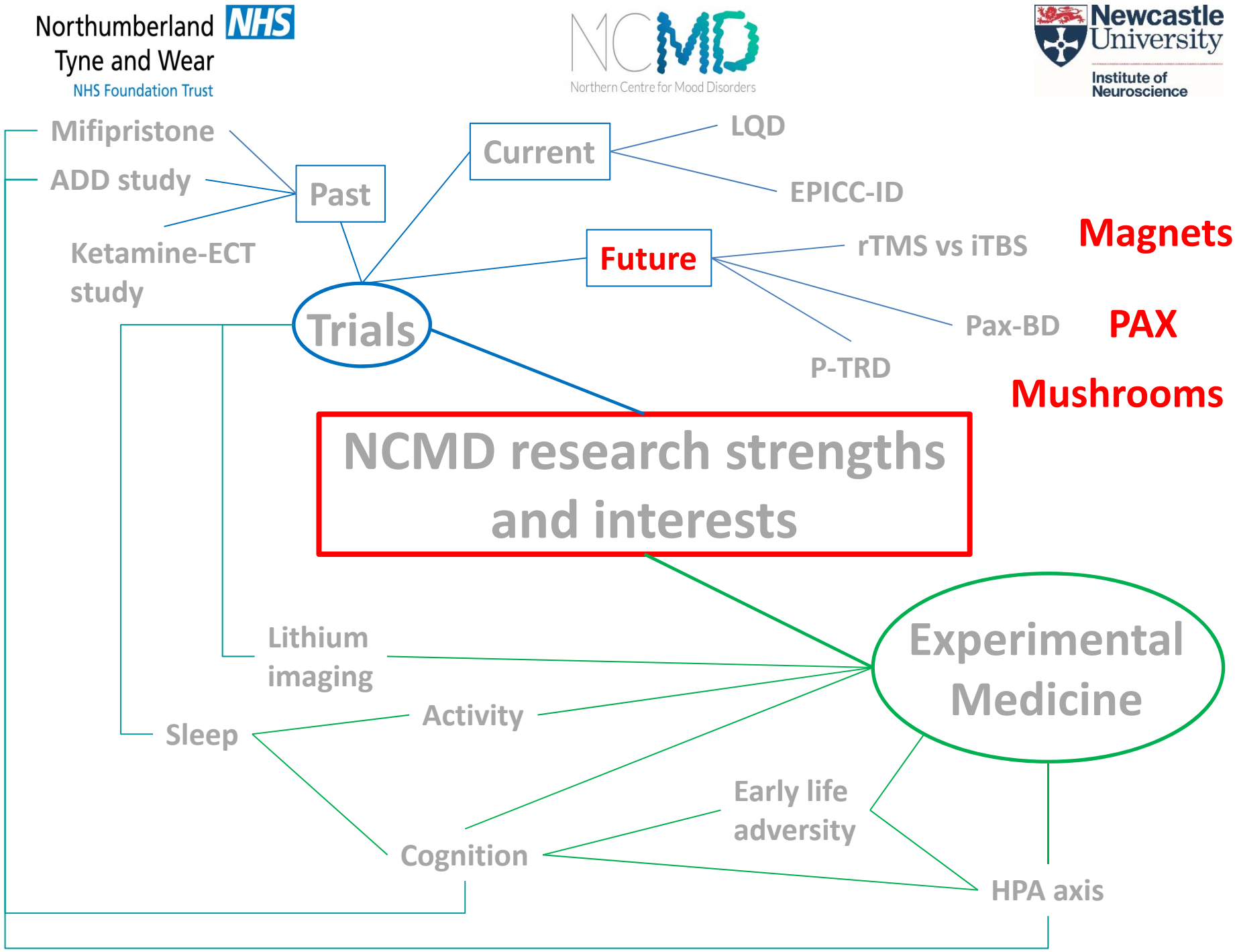
Pramipexole for bipolar depression



Zarate et al. 2004 Biol Psych *56:54-60*

Pax-BD: Randomised placebo controlled trial of Pramipexole addition to mood stabilisers for treatment resistant bipolar depression

- NIHR HTA funded RCT. Led from Newcastle
- Patients with **bipolar depression** that has **not responded to at least one NICE recommended treatment**
- Aim to recruit 400+ and randomise 290 patients from 40+ Trusts across UK
- NB can't be on antipsychotics. If patients are, these will be withdrawn during a pre-randomisation phase
- Must be on a 'mood stabiliser'. If not, this will be started in a pre-randomisation phase
- Data collected remotely
- Primary outcome measure at 12 weeks but follow up for 1 year
- Recruitment **due to start in Aug/Sept**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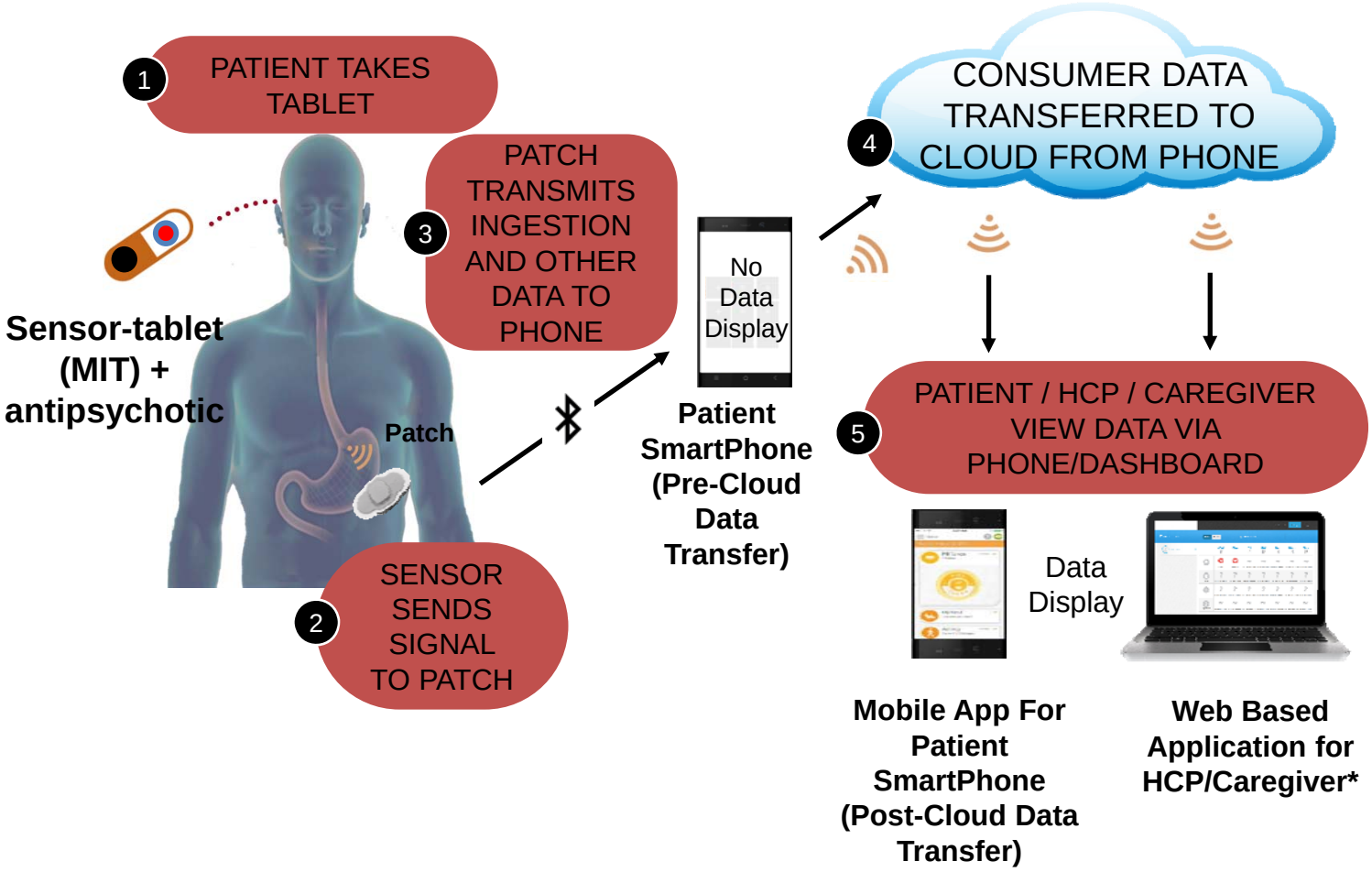
Pax, Magnets and Mushrooms…… and chips

- Digital medicine study starting in the spring
- Need a team of community consultants
- If interested see Rajesh Nair, Stuart Watson, Wendy Hall



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Conclusions

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- The last 12 months has been a very successful period for NCMD attracting national grant funding
- There are a number of important studies that are going to be starting in 2018
  - iTBS vs rTMS for unipolar depression
  - P-TRD for unipolar depression
  - PAX-BD for bipolar depression
  - Chip study for patients on antipsychotics
- We will be seeking patients for these studies and clinicians to be involved (e.g. the chip study)

- NOTE – I have not covered all work done within NCMD, in particular I have focused on work in adults