Prescribing in Early Psychosis: Make Haste Slowly

Al Powers, M.D., Ph.D.
Department of Psychiatry
Yale University School of Medicine

"Who Said the Voices Aren't Real?"
Northern Rivers Family of Services
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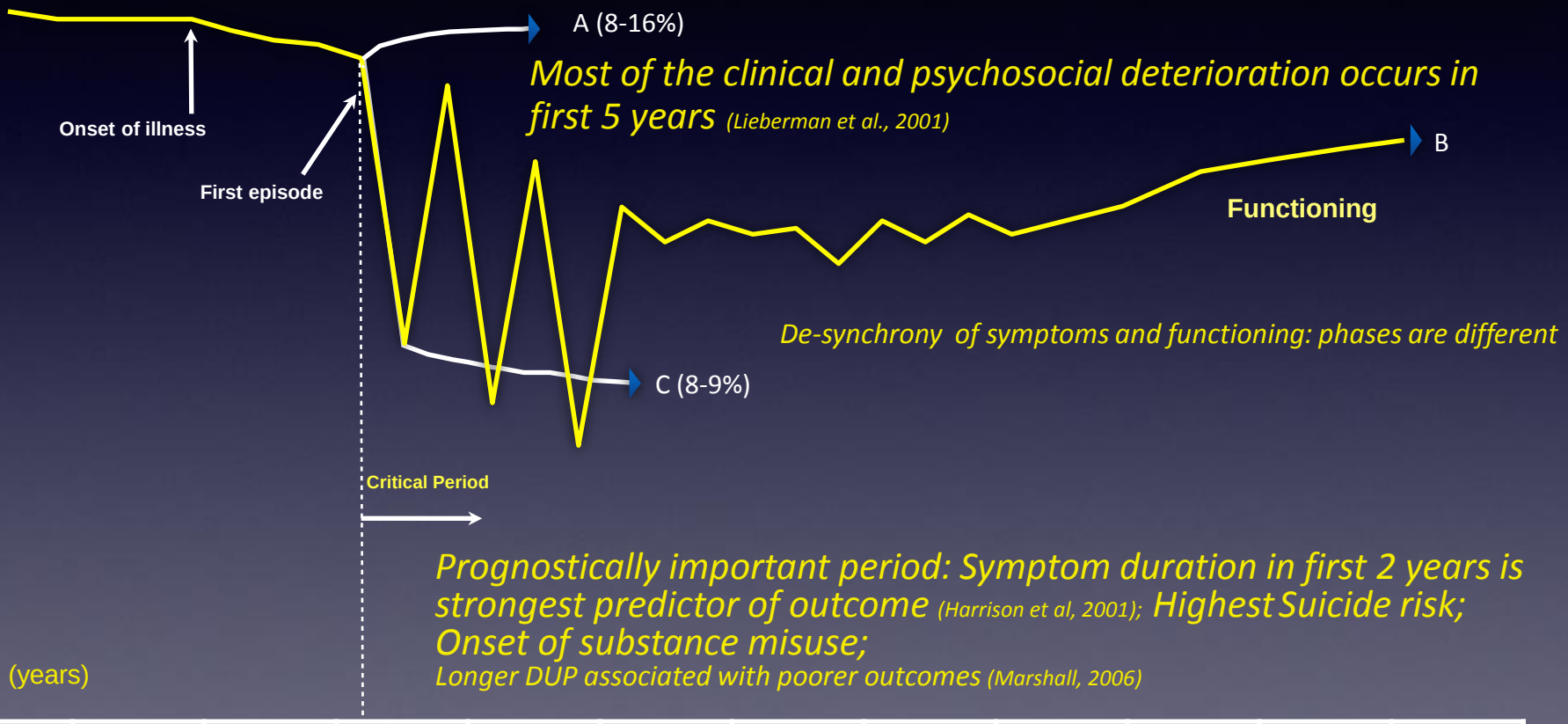
Outline

- Natural history of psychosis
- Why prescribe?
- Barriers to recovery
- One solution: A team-based approach
- What if it doesn't work?
- ? Future approaches to psychotic symptoms and med management

Course of the Primary Non-Affective Psychoses:
The Schizophrenia(s)

Phase of illness

Premorbid Prodrome Acute Plateau / Chronic



Primary Secondary Tertiary Prevention

from Srihari et al. Psych Clin of N America, 2012

Why Prescribe?

- To promote recovery
- To achieve higher quality of life (QOL):
  - Two recent studies showed significantly greater improvement in QOL than those treated with placebo.
  - One of these found that long-acting risperidone (25 mg q 2 weeks) improved QOL to levels “not significantly different from normal.”
- Medication is a tool in a holistic treatment approach aimed at recovery:
  - Can allow for engagement with other specialties focused on minimizing decrements in QOL and overall potential

1. Hamilton SH, Revicki DA, Genduso LA, Beasley CM. (1998), *J Clin Psychopharmacol.*

2. Nasrallah HA, Duchesne I, Mehnert A, et al. (2004) *J Clin Psychiatry*.

Barriers To Recovery

- Failure to engage
  - Difficulty accepting new diagnosis of a serious mental illness
  - Stigma associated with illness
  - Fear of loss of freedom

- Non-adherence
  - 25-50% of people with schizophrenia are believed to be non-adherent with maintenance therapy[1]

1. Nosé et al. (2003) *PsychMed*

Prescribing in First-Episode Psychosis: A Team-Based Approach

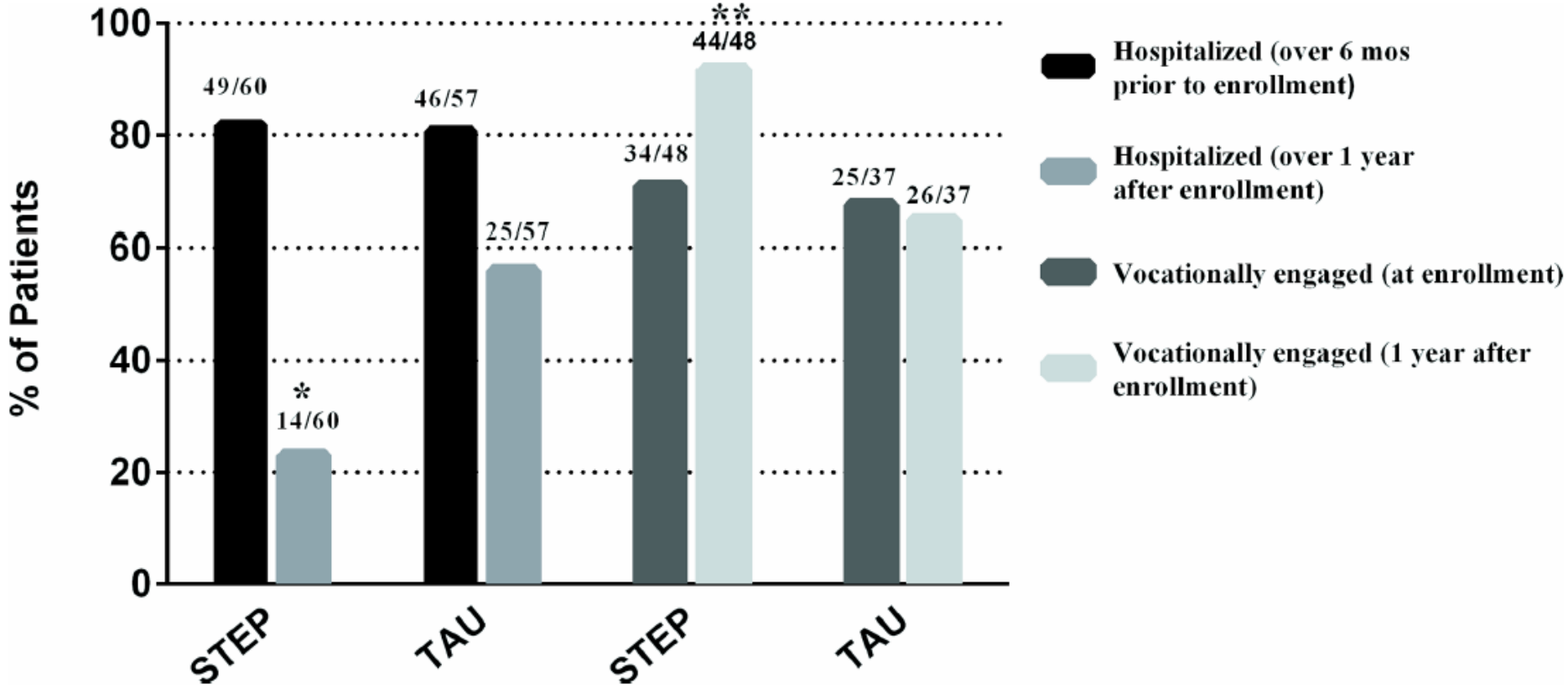
Prescribing in First-Episode Psychosis: A Part of Coordinated Specialty Care (CSC)

- A recovery-oriented treatment program for people with first episode psychosis (FEP), valuing:
  - Shared decision-making
  - Personalized treatment planning, targeting patient-identified goals
  - Utilization of a multidisciplinary team to offer comprehensive care for FEP

Prescribing in First-Episode Psychosis: A Part of Coordinated Specialty Care (CSC)

- Parts of CSC might include:
  - Medication management
  - Individual psychotherapy
  - Family psychoeducation
  - Case management
  - Supported employment/education services

Does CSC work?



Kane, et al (2015) *Am J Psychiatry*

Why does it work?

- Is this adherence therapy?
  - No
  - Adherence therapy widely discredited as ineffective
- Patient-centered, allows identification of patient goals, and enhanced engagement

What is a prescriber's role in CSC?

- Patient, non-judgmental listening and development of a differential diagnosis
- Determination of patient's goals
- Offering health-related services to aid with achieving those goals
  - Screening for secondary causes of psychosis (labs, imaging, referral to specialty services as indicated)
  - Pre-medication screening
  - Starting medications in a way that maximizes long-term adherence
  - Performing routine maintenance to troubleshoot, manage adverse effects

Diagnostic Assessment

Brain on Fire: Anti-NMDA, A Clinical and Case perspective

Susannah Cahalan, Writer and Journalist

Secondary Psychosis

- Consider life-threatening causes (delirium, including EtOH w/d)
- Consider easily diagnosed and treatable (e.g. syphilis, thyroid)
- Consider common (primary)
- Remain alert for uncommon presentations of illnesses requiring different Rx (e.g. epilepsy)

Sources: Coleman & Gillberg (1996), Coleman & Gillberg (1997),Goff et al. (2004), and Hyde & Lewis (2003).

Epilepsy
Head trauma (history of) Dementias
Alzheimer's disease
Pick's disease
Lewy body disease
Stroke (only rarely associated with psychosis)

Psychosis Associated with Medical Diseases

Space-occupying lesions and structural brain abnormalities
Primary brain tumors Secondary brain metastases Brain abscesses and cysts Tuberous sclerosis
Midline abnormalities (e.g., corpus callosum agenesis, cavum septi pellucidi) Cerebrovascular malformations (e.g., involving the temporal lobe)
Hydrocephalus
Demyelinating diseases
Multiple sclerosis (not typically associated with psychosis)
Leukodystrophies (metachromatic leukodystrophy, X-linked adrenoleukodystrophy, Marchiafava-Bignami disease) Schilder's disease
Neuropsychiatric diseases
Huntington's disease
Wilson's disease
Parkinson's disease (not typically associated with psychosis unless treated)
Familial basal ganglia calcification
Friedreich's ataxia
Autoimmune diseases
Systemic lupus erythematosus Rheumatic fever Paraneoplastic syndrome
Myasthenia gravis
Infections
Viral encephalitis (e.g., herpes simplex, measles [including subacute sclerosing panencephalitis], cytomegalovirus, rubella, Epstein-Barr, varicella) Neurosyphilis
Neuroborreliosis (Lyme disease) HIV infection or AIDS
CNS-invasive parasitic infections (e.g., cerebral malaria, toxoplasmosis, neurocysticercosis) Tuberculosis
Sarcoidosis
Cryptococcus infection
Prion diseases (e.g., Creutzfeldt-Jakob disease) Endocrinopathies
Hypoglycemia Addison's disease Cushing's syndrome
Hyper- and hypothyroidism Hyper- and hypoparathyroidism
Hypopituitarism
Narcolepsy
Nutritional deficiencies Magnesium deficiency Vitamin A deficiency Vitamin D deficiency Zinc deficiency
Niacin deficiency (pellagra)
Vitamin B_{12} deficiency (pernicious anemia)
Metabolic diseases (partial list)
Amino acid metabolism (Hartnup disease, homocystinuria, phenylketonuria)
Porphyrias (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria) GM-2 gangliosidosis
Fabry's disease
Niemann-Pick type C disease
Gaucher's disease, adult type
Chromosomal abnormalities
Sex chromosomes (Klinefelter's syndrome, XXX syndrome) Fragile X syndrome
Velocardiofacial syndrome

Pragmati

c Work-Up vs. the Quest for Certainty

1. Test for common disorders, co-morbidities
2. Revisit treatable secondary causes (but consider risks/costs of testing)
3. Test for rare but more easily treatable disorders
4. Establish baseline cardiovascular risk (and monitor!)

TABLE 5. Medical work-up for first-episode psychosis

Physical exam with emphasis on neurological exam
Vital signs
Weight and height (BMI), waist circumference
ECG (if cardiac risk)

Laboratory tests

Broad screening and medical baseline:
- CBC
- Electrolytes including calcium
- Renal function tests (BUN/creatinine)
- Liver function tests
- Erythrocyte sedimentation rate
- Antinuclear antibody
- Fasting glucose
- Lipid profile
- Consider prolactin level
- Consider hepatitis C (if risk factors)
- Pregnancy test (in women of child-bearing age)
- Urine drug screen

Exclude specific treatable disorders:
- TSH
- FTA-ABS (fluorescent treponemal antibody absorbed)
- HIV test
- Ceruloplasmin
- Vitamin B12

Neuroimaging

MRI (preferred over CT)

Ancillary tests

Expand aetiological search if indicated, taking into account epidemiology:
For example, CXR, EEG, lumbar puncture, karyotype, heavy metal testing
Expand medical monitoring if indicated:
For example, eye exam (if risk factors for cataracts)

Freudenreich et al. Early Interv Psychiatry 2009; 3:10-18.

Diagnostic Assessment
Summary/Principles

1. Take a Bayesian perspective

- Knowledge of horses and zebras: educated prior probability
- Critical interpretation of tests (labs, imaging, exams)
- Tests perform differently at different base prevalence rates

2. Probabilistic, revisionist approach (vs. diagnostic certainty)

3. Longitudinal f/u + capacity to be surprised

Pre-Medication Screening

- Good PMH
- Consider:
  - CBC
  - Lipids
  - LFTs
  - TFTs

Targets of Medication Treatment

1. 'Positive' symptoms: 'Psychosis'

- Reality distortion (delusions, hallucinations)
- Disorganization (thought, behavior, expression of feeling)

2. 'Negative' symptoms

- lack of motivation (*avolition*)
- reduction in spontaneous speech (*alogia*)
- social withdrawal (*apathy*)

Loss of anticipatory but not consummatory pleasure

Targets of Medication Treatment

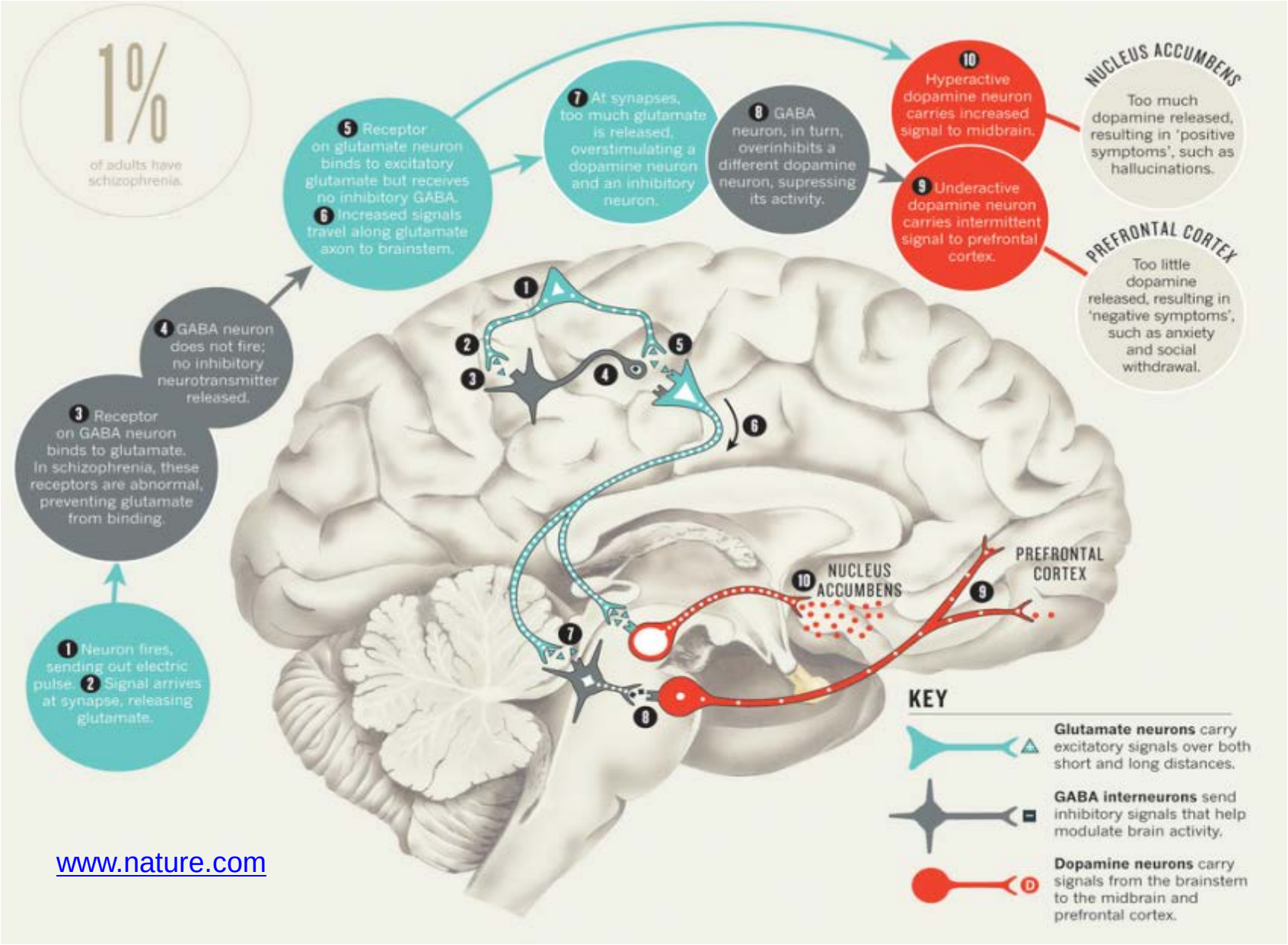
3. Cognitive deficits

- Memory (working and long term)
- Attention, processing speed
- Executive functioning
- Social cognition

4 & 5. Affective dysregulation

- Depressive symptoms
- Manic symptoms

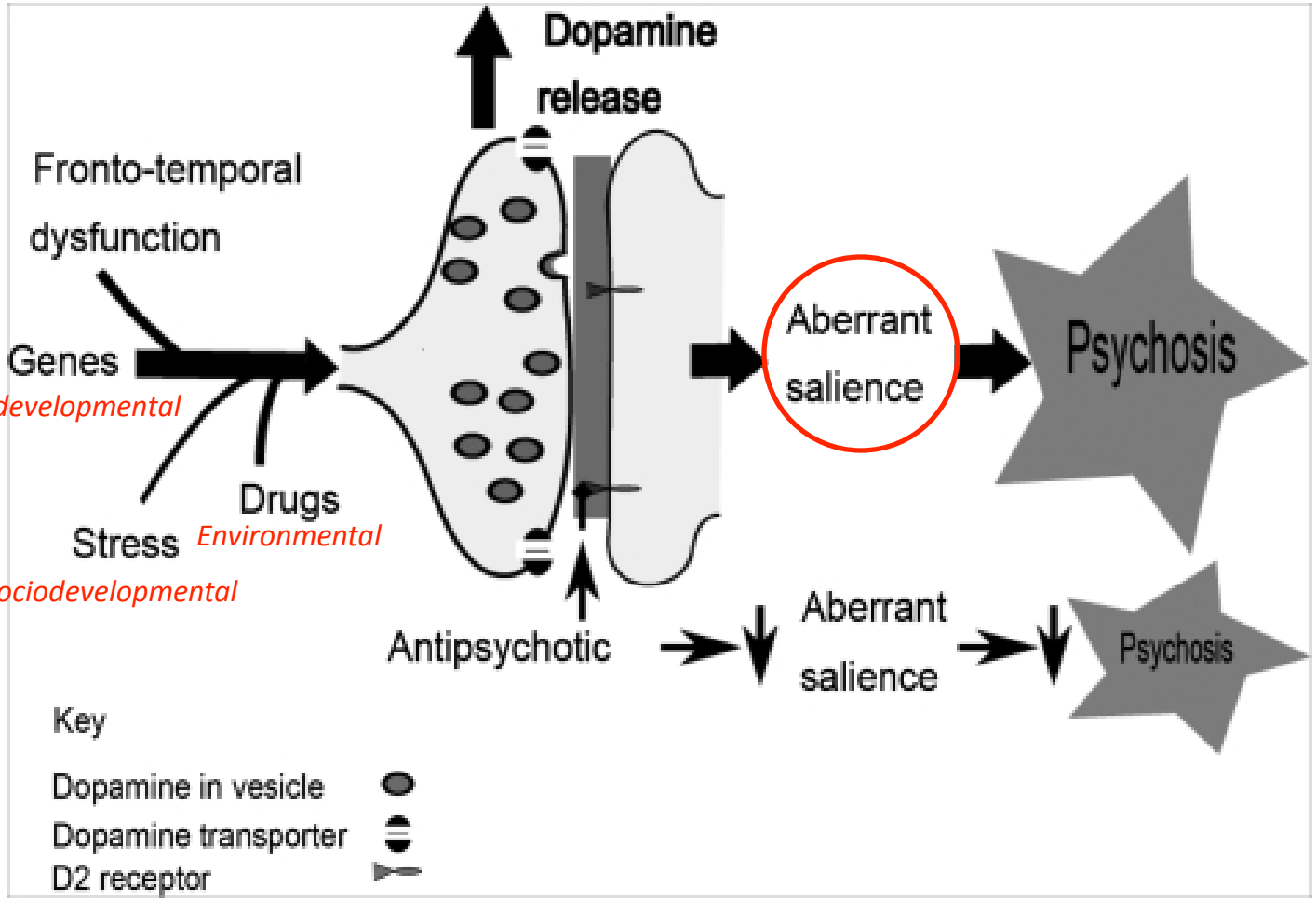
Neurochemistry of Schizophrenia: Glutamate, GABA, Dopamine, ….



www.nature.com

The Dopamine Model - Updated

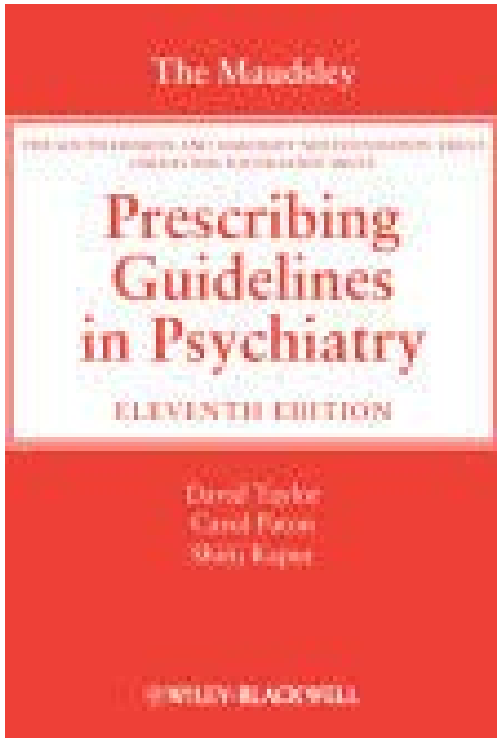
The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway. Howes & Kapur Schiz Bull 2009



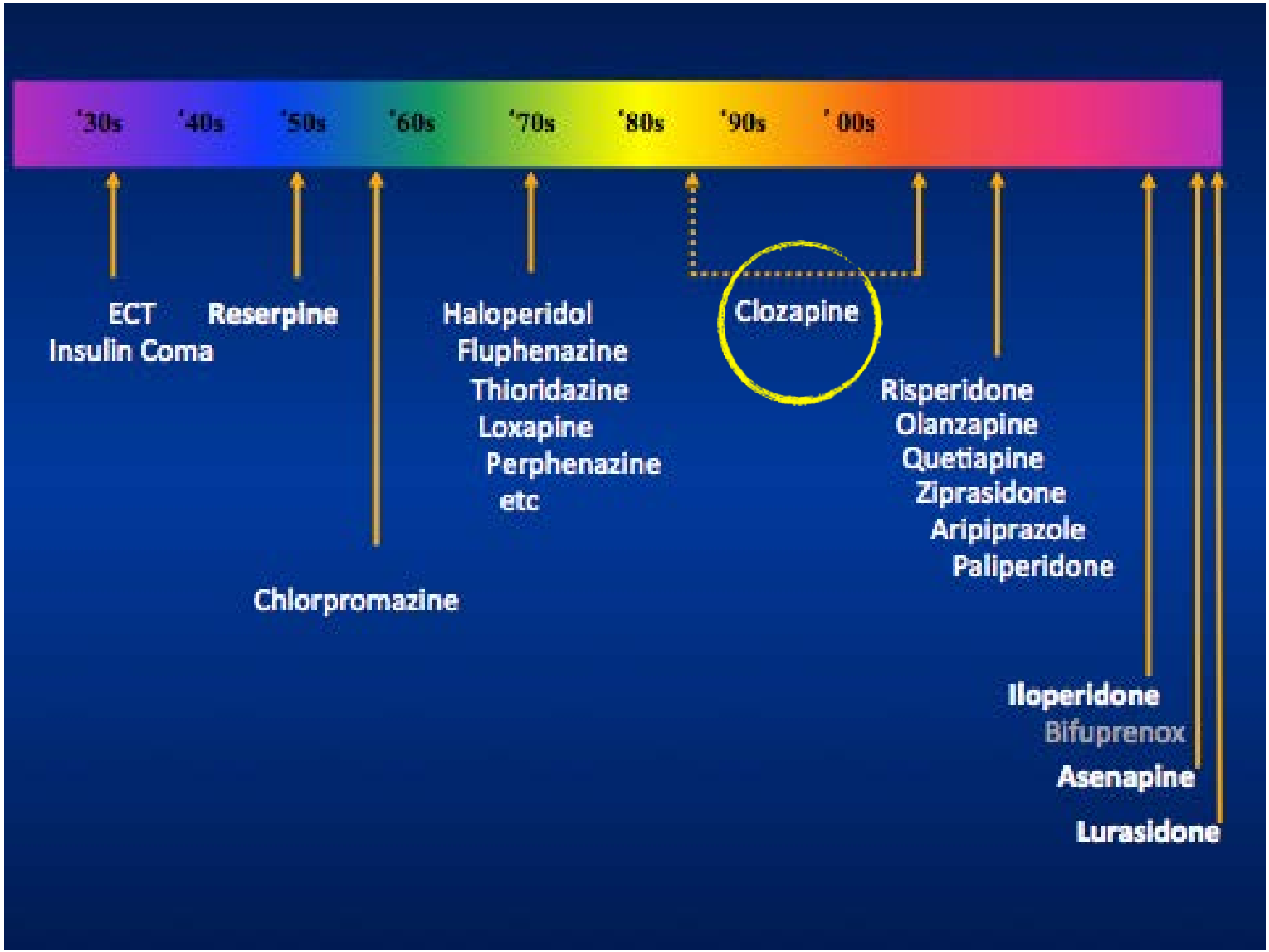
Schizophrenia: an integrated sociodevelopmental-cognitive model. The Lancet 2014; 383:1677–1687

Treating with Antipsychotic medications

- Which medication(s)?
  - FGA (high vs. low potency) vs. SGAs or better: 'Dopamine receptor antagonists' with variable side effect profiles
- How to dose?
- For how long?
- Common side effects?

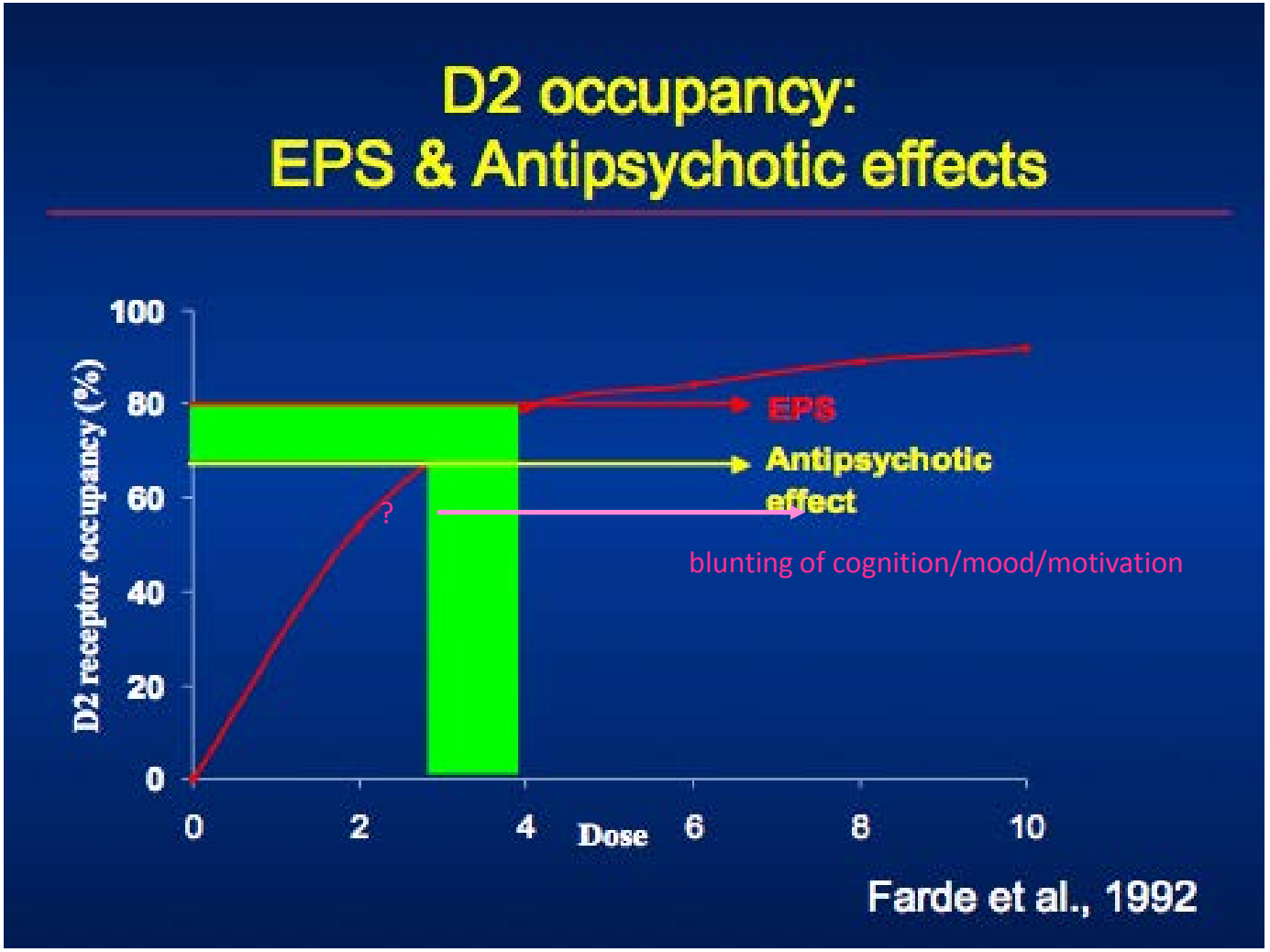


Antipsychotic medications: which one?



from D. Cyril D'Souza

Antipsychotics: Dose matters



Large (30-80%) variability in dose-to-occupancy correlation: search for easy effective dose

Antipsychotic medications: what dose?

Drug	ED_{50}	Near-maximal Effective Dose
FGAs		
Chlorpromazine	150 mg/d	400–450 mg/d
Haloperidol	0.5–2 mg/d	3.5–10 mg/d
Haloperidol decanoate	25 mg/mo	100–200 mg/mo
Trifluoperazine	—	10–15 mg/d
Thiothixene	—	<10 mg/d
Fluphenazine	—	<6.9 mg/d
Fluphenazine decanoate/enanthate	—	25 mg/2 wk
SGAs		
Olanzapine	9 mg/d	>16 mg/d
Olanzapine IM	>6 mg/d	>10 mg/injection
Risperidone	2 mg/d	4 mg/d
Risperidone depot	15 mg/mo	50 mg/mo
Amisulpride	50 mg/d	200 mg/d
Aripiprazole	<1.5 mg/d	10 mg/d
Quetiapine	80–215 mg/d	150–600 mg/d
Remoxipride	60 mg/d	120–240 mg/d
Sertindole	10 mg/d	12–20 mg/d
Clozapine	—	>400 mg/d
Ziprasidone, acute	63 mg/d	120–160 mg/d
Ziprasidone, maintenance	40 mg/d	80–160 mg/d

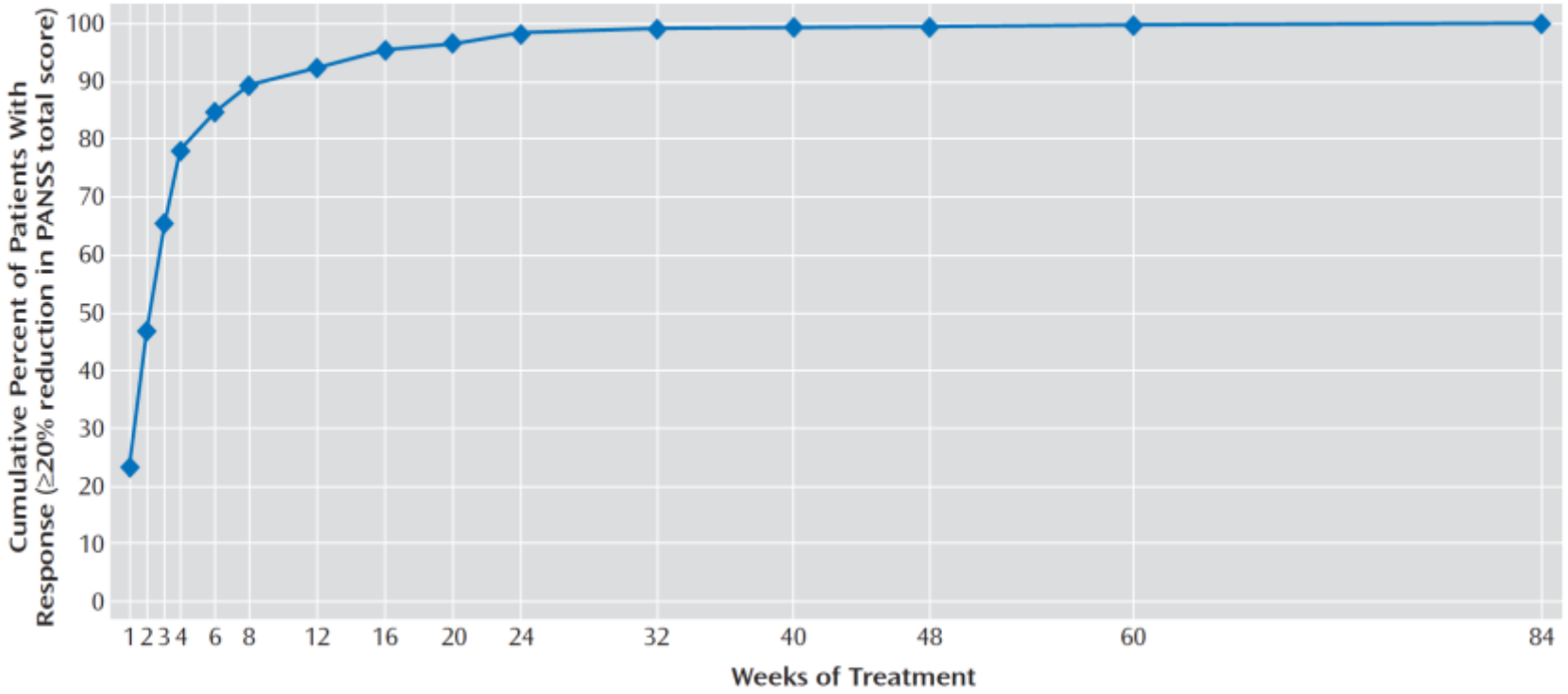
Davis & Chen, J of Clin Psychopharm, 2004;

Drug	Minimum Effective Dose
Amisulpride	–
Aripiprazole	10
Asenapine	10
Clozapine	300?
Haloperidol	4 (4.5)
Iloperidone	8[a] (12)
Lurasidone	40
Olanzapine	7.5 (10)
Paliperidone	3 (6)
Quetiapine	150 (250)
Risperidone	2 (4)
Sertindole	12 (16)
Ziprasidone	40 (80)
Zotepine	–

Leucht et al. Schiz Bulletin 2014 &
Woods SW. *J Clin Psychiatry* 2003;64:663–667.

How Long?

FIGURE 1. Time Until ≥20% Reduction in Total Score on the Positive and Negative Syndrome Scale After Initiation of Treatment With Risperidone or Haloperidol Among 522 Patients With First-Episode Schizophrenia



Clinical response (not remission). Overall, 77% responded over median of 206 days.

Emsley Am J Psych 2006

Make Haste…Slowly

Why make haste?

- Because decreasing DUP is important for maximizing outcomes

Why slowly?

- Therapeutic alliance is still the best protection against non-adherence
- There may be some lack of insight into the presence of a mental illness and the relevance of drug treatment.
  - Despite this, there are likely points for common engagement:
    - Reducing stress
    - Improve sleep
    - Improve appetite
    - Addressing distressing symptoms: hallucinations, delusions, disorganization
- Adequate discussion of potential effects and adverse effects takes time, and tailoring adverse effect profile to patients takes discussion
- Starting at a low dose allows monitoring for early emergence of side effetcts like EPS and weight gain

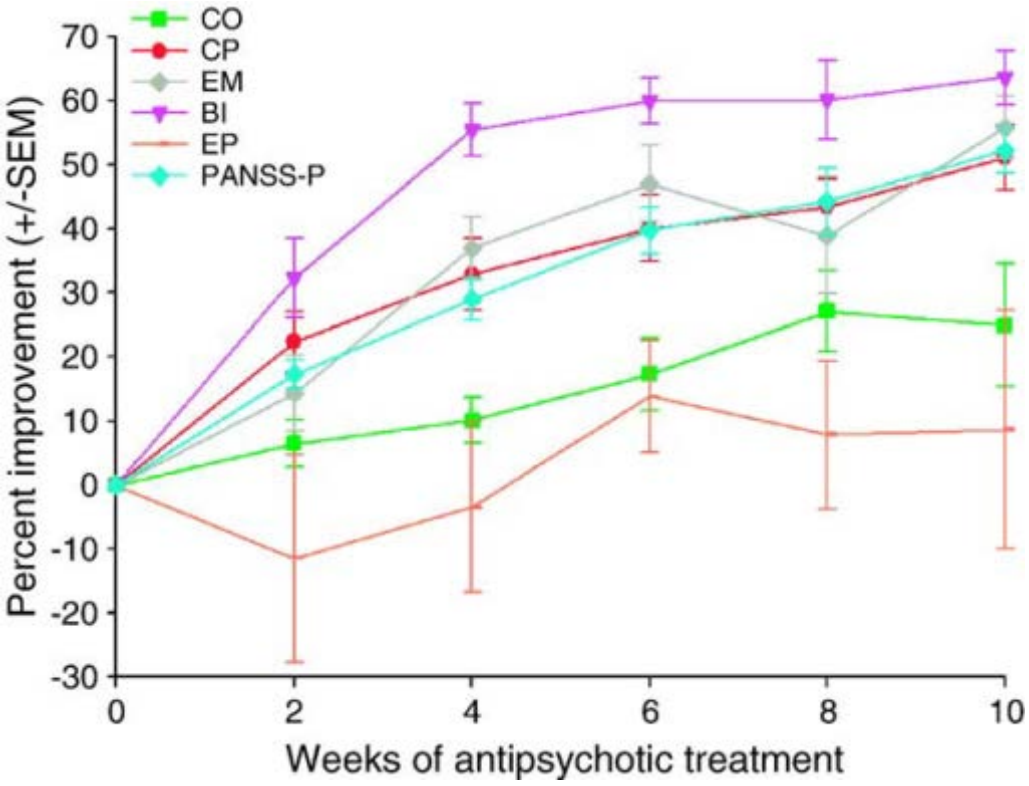
Principles of Treatment:

1. Maximize tolerability & adherence in service of positive symptom remission & relapse prevention: finding the window of D2 blockade (60-70%)

- Lethargy, sedation, sexual dysfunction: drop dose or switch
- Parkinsonism, akathisia, dystonia (acute EPS): anticholinergics/benzodiazepines, dose, switch
- Tardive Dyskinesia: ? dose related, no established Tx, Clozapine is lower risk (and *maybe* other SGAs)
- Minimize adverse effects on cognition, mood, motivation: dose, but may be inevitable for some…

Use the least effective dose and proactively address side effects

What do antipsychotic medications do to the subjective experience of psychosis ?



from Mizrahi et al. Schiz Research 2006

1. **B**ehavioral **I**mpact of the experience
2. **EM**otional involvement
3. **C**ognitive **P**reoccupation with the psychotic experience
4. **CO**nviction in the psychotic experience
5. **E**xternal **P**erspective about the experience

Principles of Treatment:

2. Address Cardiovascular Risk in your treatment approach

- FGAs - slightly higher risk of EPS (except low-potency FGAs) and TD but better CV profile (except low potency FGAs)
  - *Abilify and Ziprasidone appear to have lower metabolic burden (but most studies are short-term)
- Clozapine - reduces overall mortality (likely early suicide/accidental death advantage but increased late CV risk). Olanzapine should be reserved for those who respond to no other weight-sparing choice: AVOID AS FIRST-LINE
- Minimize polypharmacy (mood stabilizers, antidepressants, antipsychotics)
- Monitor, monitor, monitor and taper or discontinue unnecessary medications. Don't be afraid to switch off Olanzapine or Seroquel or Risp to a weight sparing alternative: even if it has been effective
- <u>Target lifestyle: smoking, exercise, diet</u>
- <u>Improve access to primary care, develop relationship with internist (e.g. Metformin for weight loss or IFG)</u>

Principles of Treatment:

3. Integrate with rehabilitation & psychotherapy:

a) core cognitive, negative (deficit) symptom domains not currently improved by medications

b) D2 blockade can cause affective flattening, reduced motivation…(dose responsive)

- Supported Employment
- Supported Education
- Supported Housing
- CBT
- Family Education & Support
- Social Skills Training
- Cognitive Remediation

Phase of Illness: Medication targets

1. ACUTE

Safety: agression/hostility

Symptoms: remission of 'positive' symptoms, mood/anxiety

Suicide, cognitive losses, stigma, substance use, -ve sx

2. STABILIZATION

Prevent relapse

Support rehabilitation

Work/school, relationships

3. RECOVERY

Prevent relapse

Maintain functioning

Cardiovascular risk

Treatment Algorithm for Primary Non-Affective Psychotic Illnesses

Stage 1: 'First-episode' Psychosis

Trial of a single SGA (except Olanzapine) or high-potency FGA *toward remission*

Consider Clozapine for recurrent suicidality/violence

Stage 2: Sub-optimal Response

Second trial of SGA or FGA (*toward remission*)

Consider Clozapine for recurrent suicidality/violence

Stage 3: Clozapine

Stage 4: Clozapine + high potency agent

Stage 5: ECT or enroll in clinical trial of new agent

Consider long acting (IM) medications at all stages for (a) non-adherence or (b) dose related side effects

Summary

- Treatment with antipsychotic medications promotes recovery and allows engagement with other important services within a coordinated specialty care (CSC) setting
- Prescribers are responsible for:
  - Patient, non-judgmental listening and development of a differential diagnosis
  - Determination of patient's goals
  - Offering health-related services to aid with achieving those goals
    - Screening for secondary causes of psychosis (labs, imaging, referral to specialty services as indicated)
    - Pre-medication screening
    - Starting medications in a way that maximizes long-term adherence
    - Performing routine maintenance to troubleshoot, manage adverse effects
- Use guidelines and team members as resources for troubleshooting

Thank You

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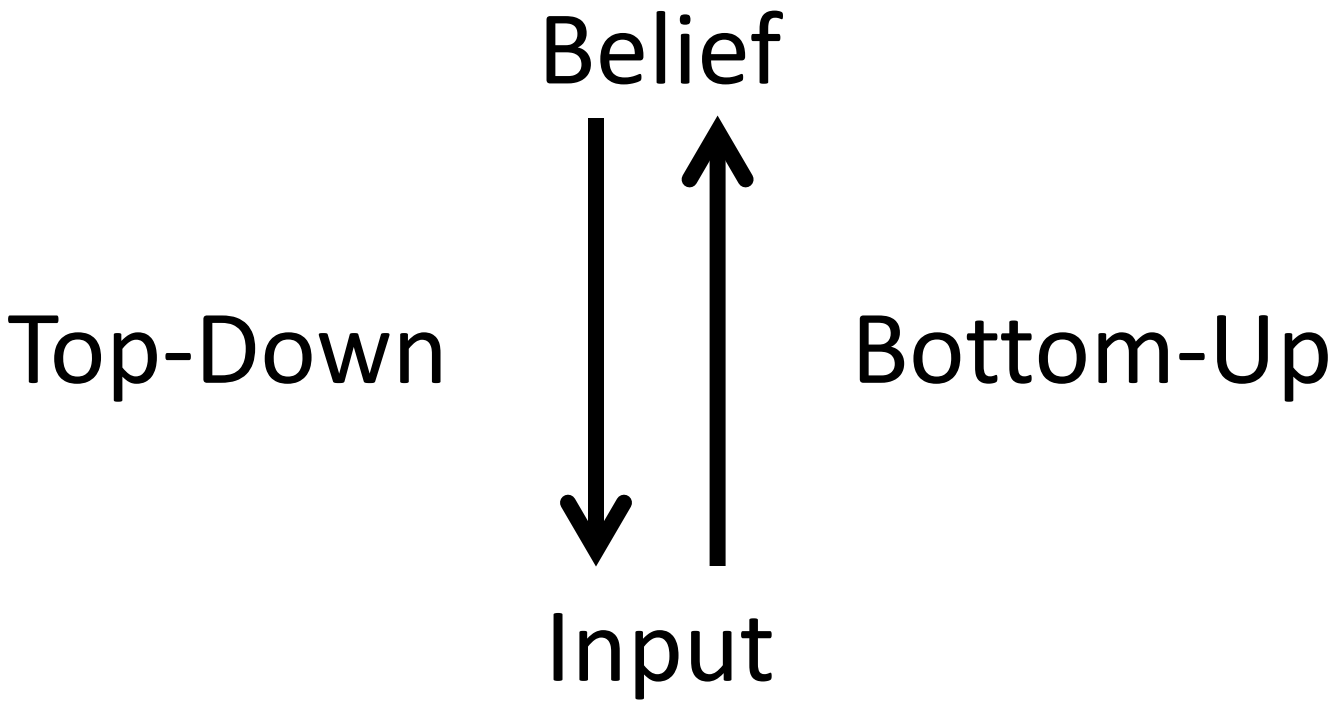
Future Directions:
Targeted Symptom-Based Treatment

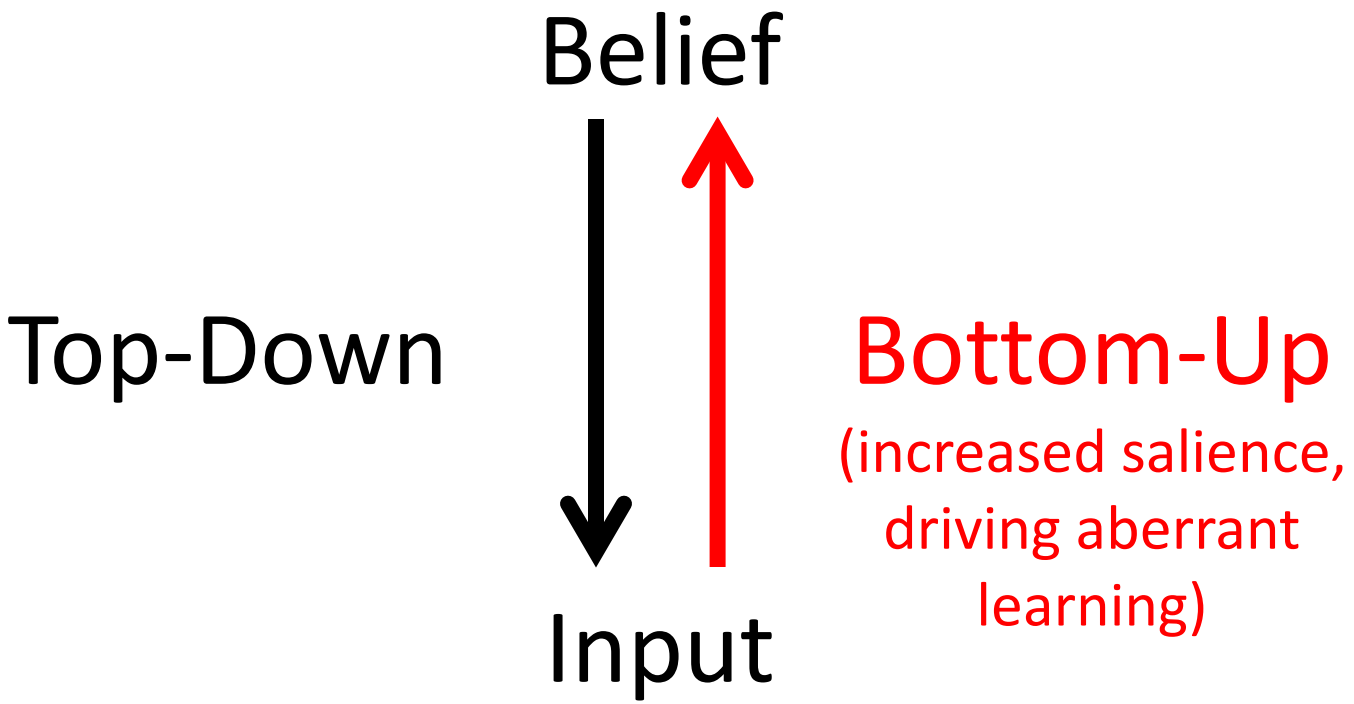
Auditory Hallucinations

- Present in roughly 70% of individuals with psychosis
- 10-30% don’t respond to antipsychotics
- Unknown neural mechanism
- Understanding auditory perception may provide insights

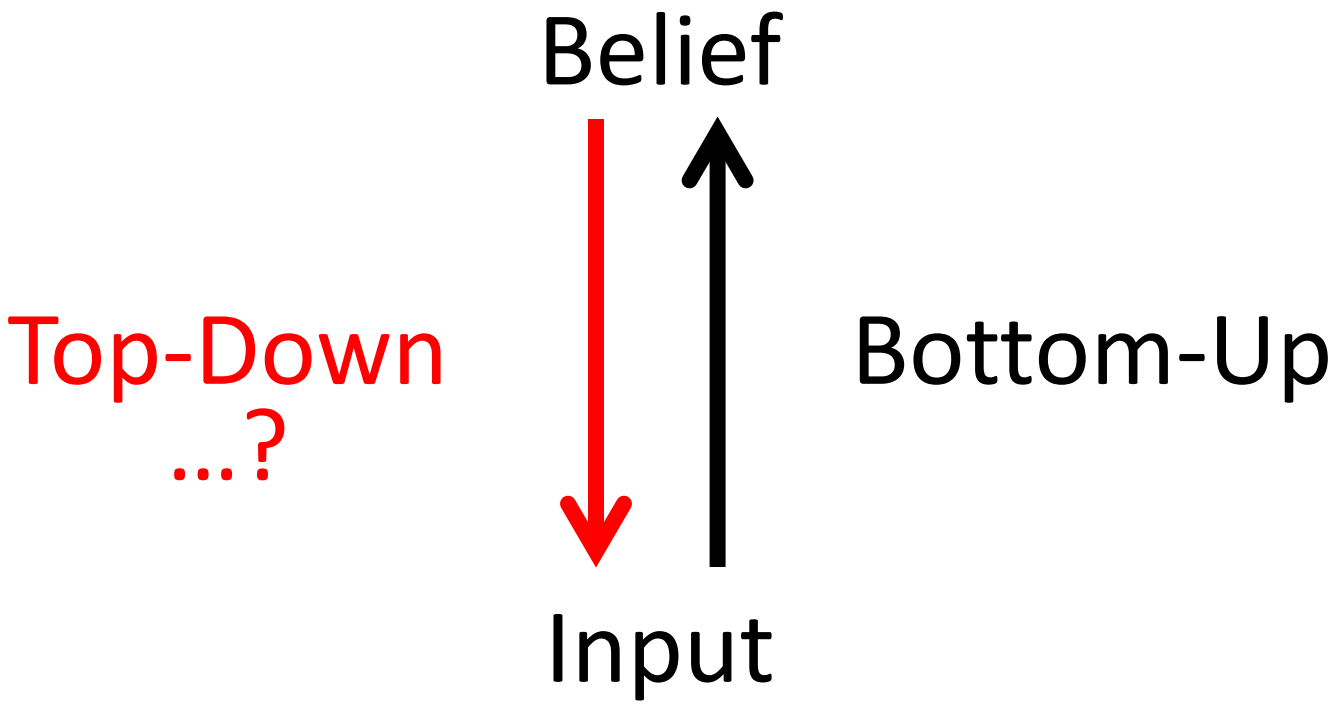
Unconscious Inference



Predictive Coding and Delusion Formation



Predictive Coding and Hallucinations



Test:
Are hallucinations produced when top-down influence is enhanced?

"Conditioned Hallucinations"

Journal of
Experimental Psychology

VOL. 28, No. 1 January, 1941

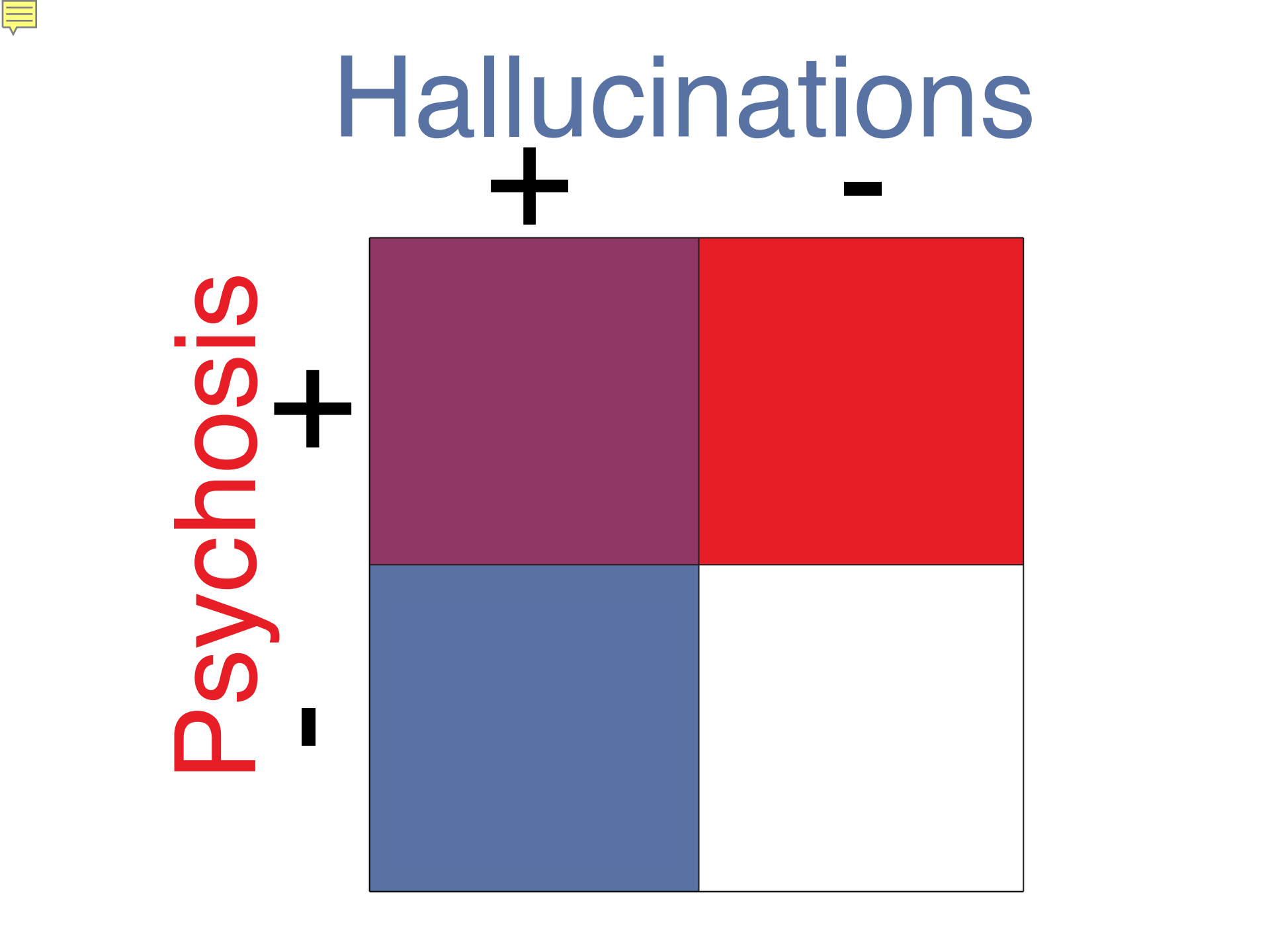
HALLUCINATIONS PRODUCED BY SENSORY CONDITIONING *

BY DOUGLAS G. ELLSON

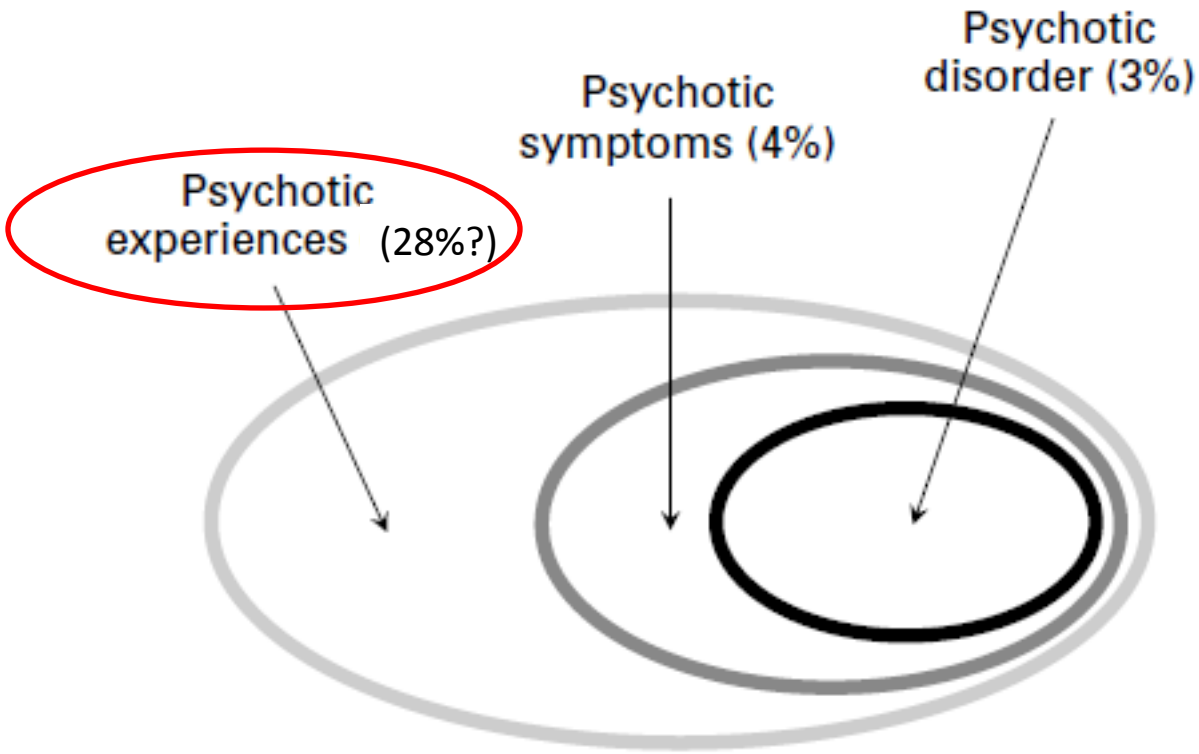
Stanford University

INTRODUCTION

The literature of 'psychic' phenomena is replete with incidents in which perceptions are reported to have occurred in the absence of physical events appropriate to evoke them. In many cases the event


Hallucinations
+
-
Psychosis
+
-

Voice-Hearing in the General Population

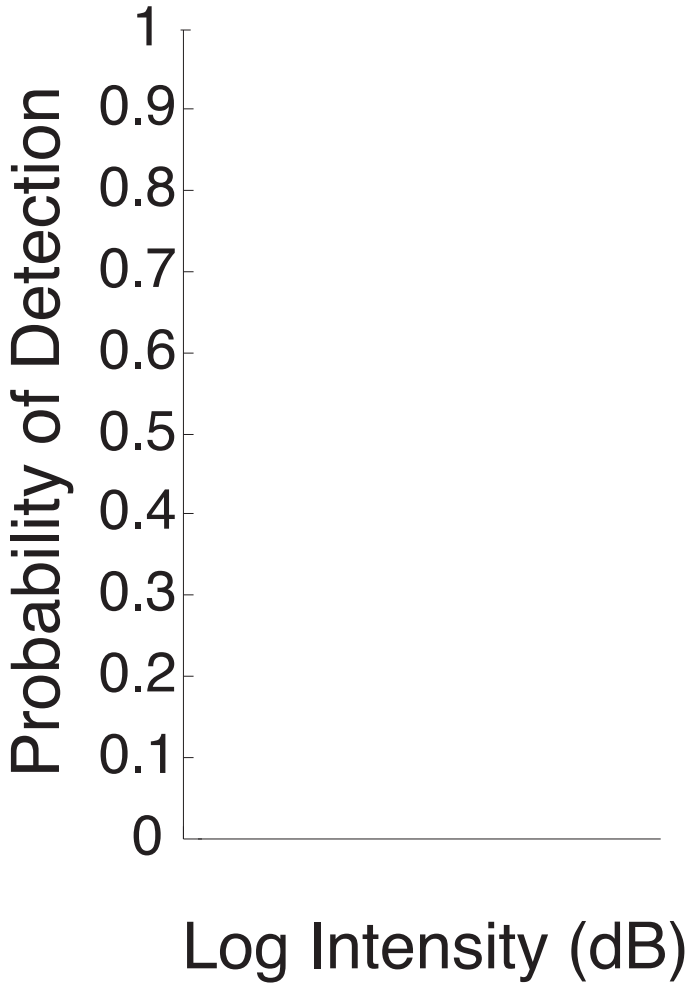


van Os et al. (2009) *Psych Med*

Phenomenological Comparison:

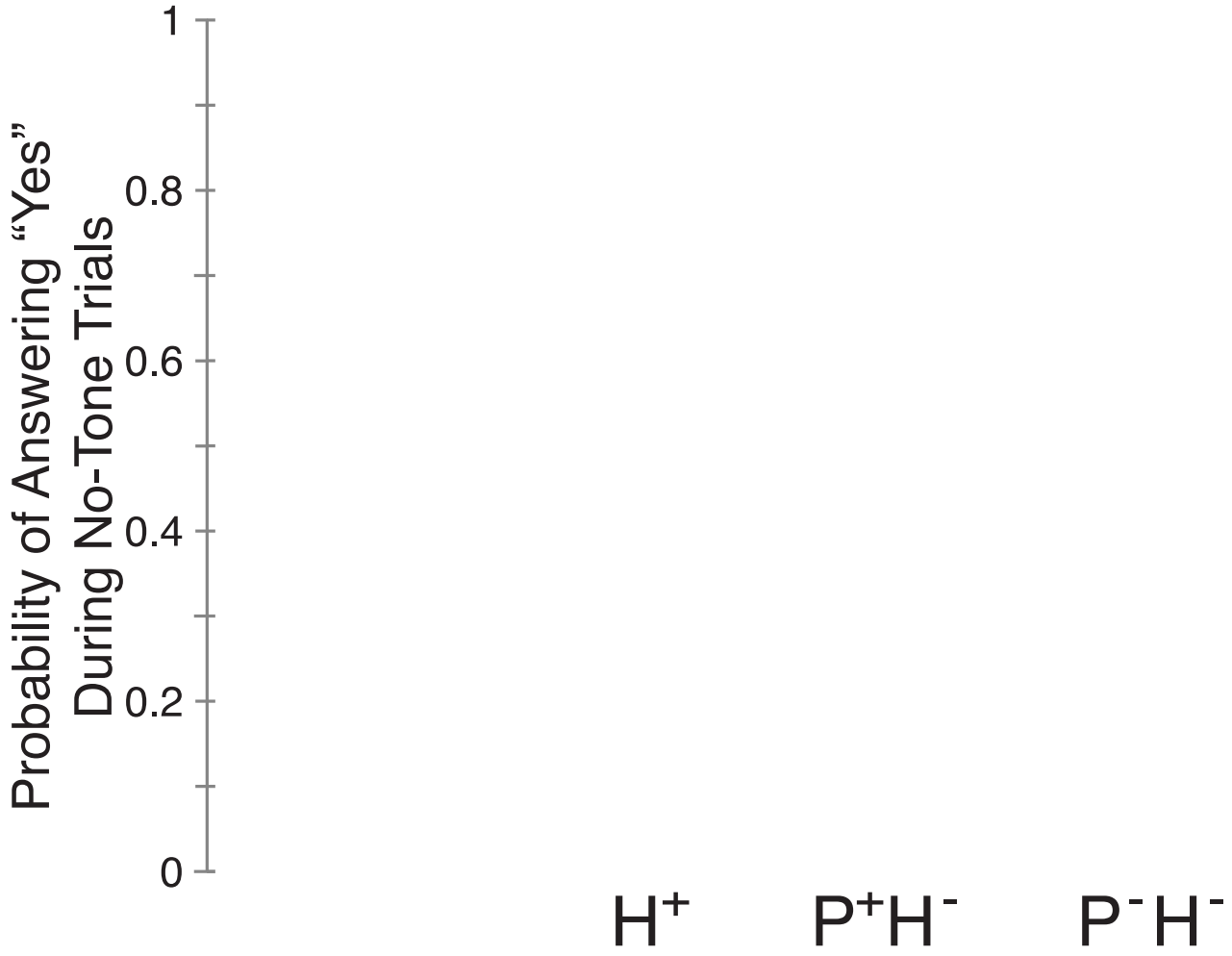
Powers, Kelley, Corlett (2017) *SchizBull*

Trial Structure of Train/Test Sequence



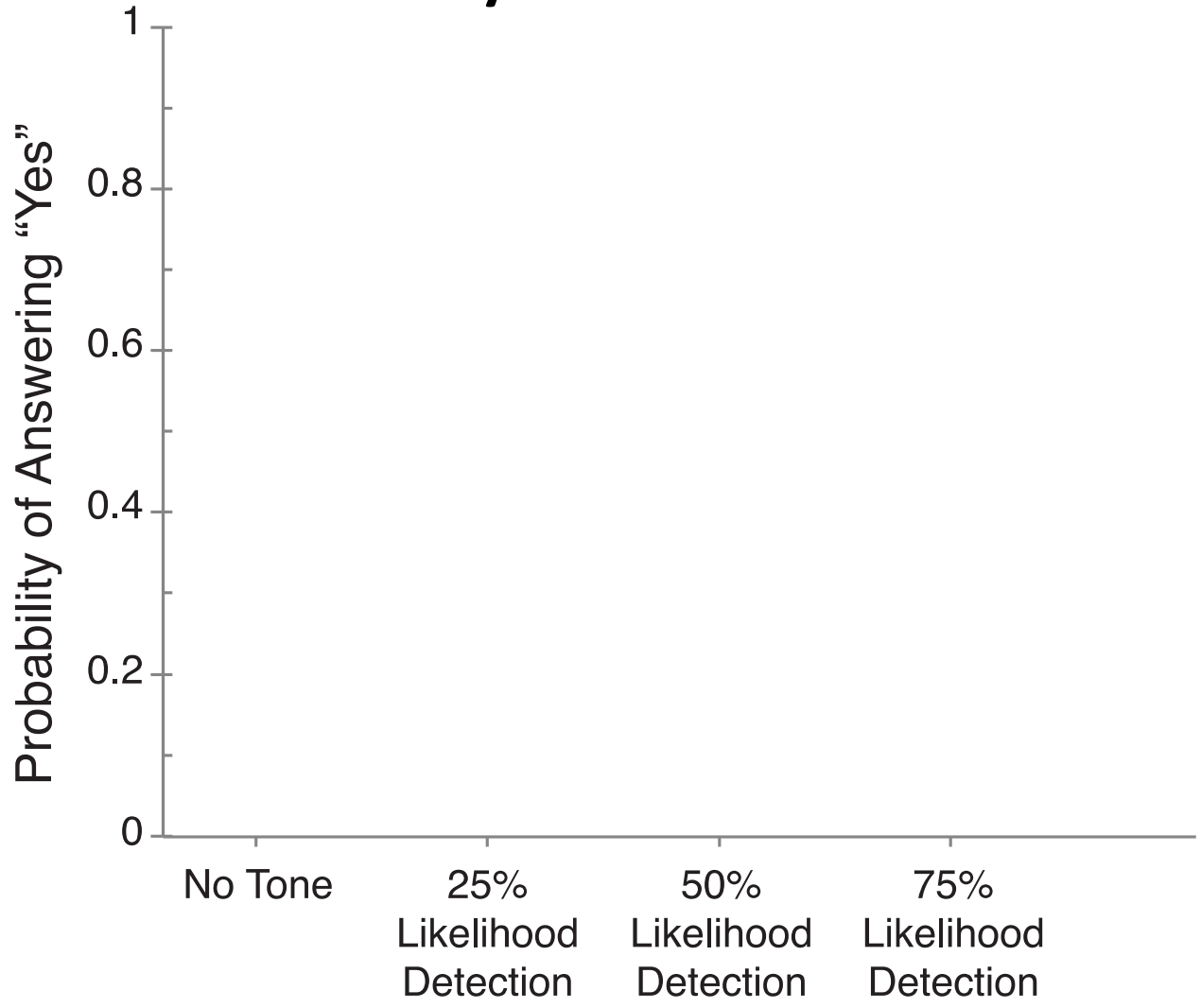
Powers, Mathys, Corlett (2017) *Science*

Likelihood of Conditioned Hallucinations by Group

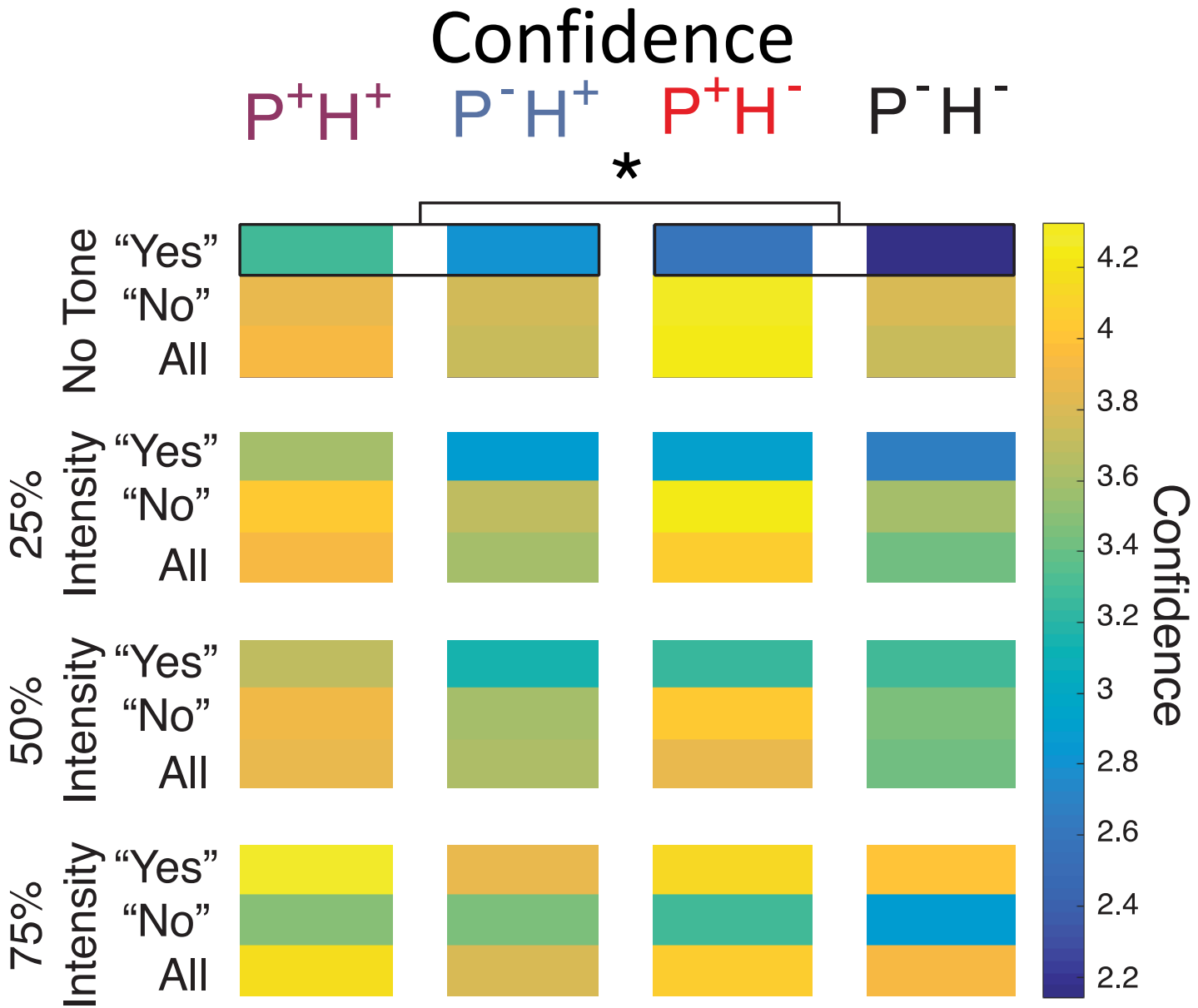


Powers, Mathys, Corlett (2017) *Science*

Likelihood of Detection By Condition



Powers, Mathys, Corlett (2017) *Science*



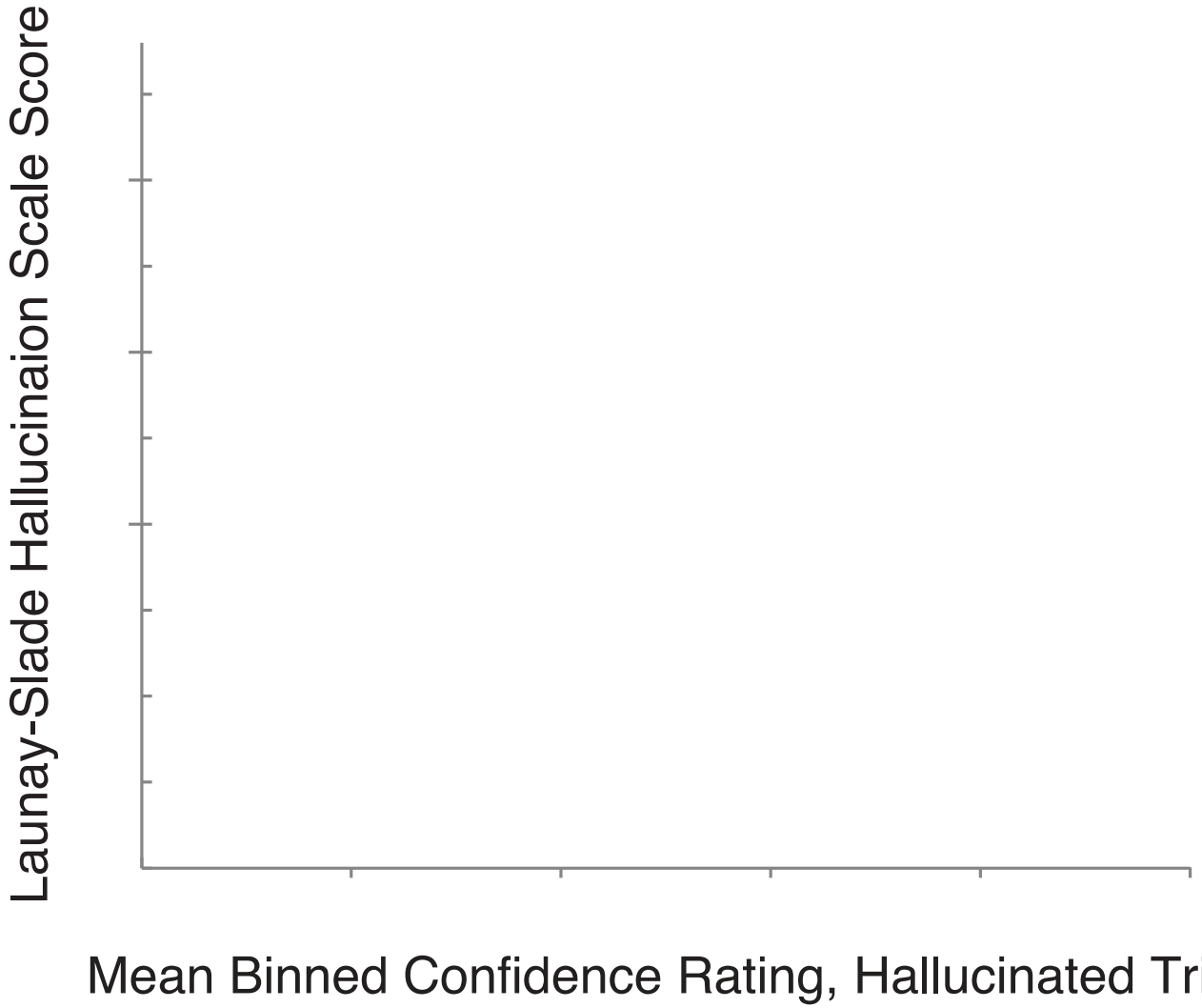
Powers, Mathys, Corlett (2017) *Science*

Proportion of Conditioned Hallucinations Correlates with Symptom Severity

Probability of Answering “Yes” on No-Tone Trials

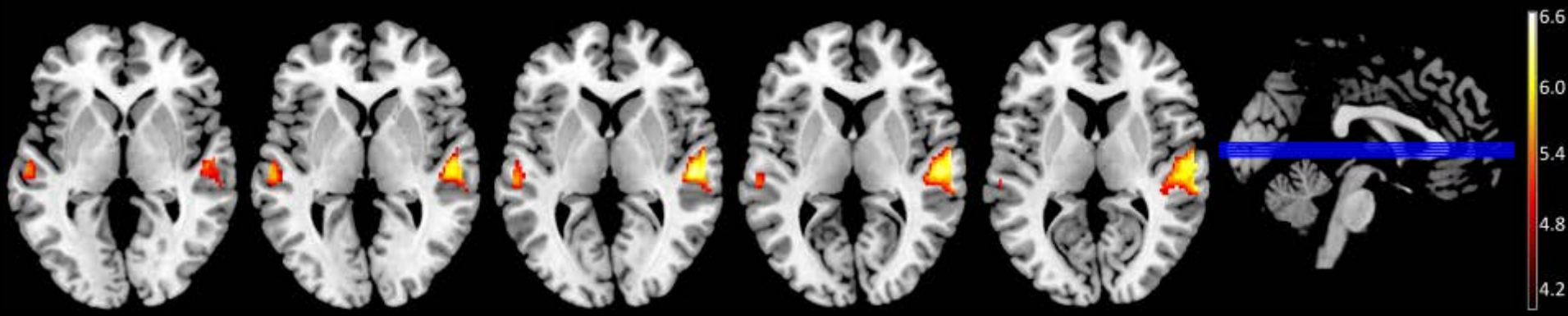
Powers, Mathys, Corlett (2017) *Science*

Confidence In Reporting Conditioned Hallucinations Correlates with Symptom Severity

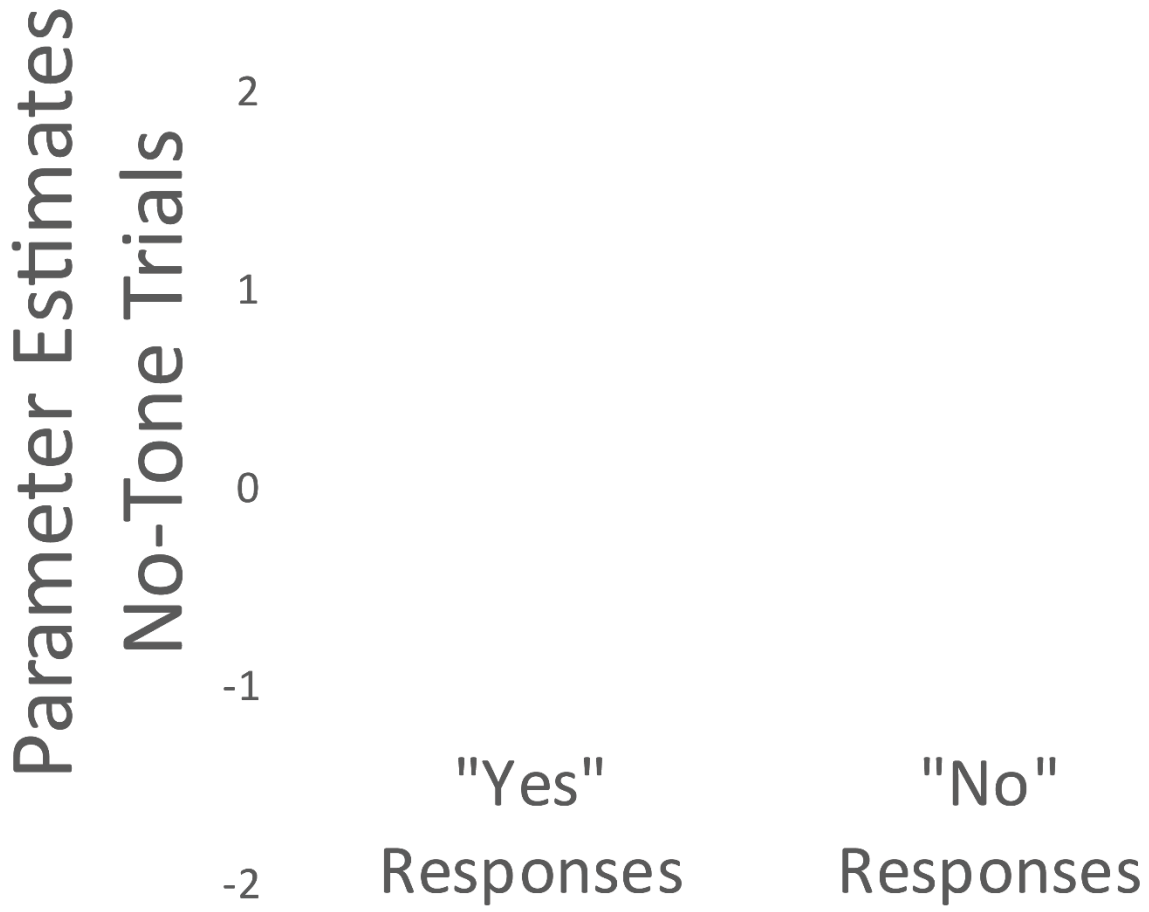


Powers, Mathys, Corlett (2017) *Science*

Imaging Results:
Tone-Responsive Region of Interest

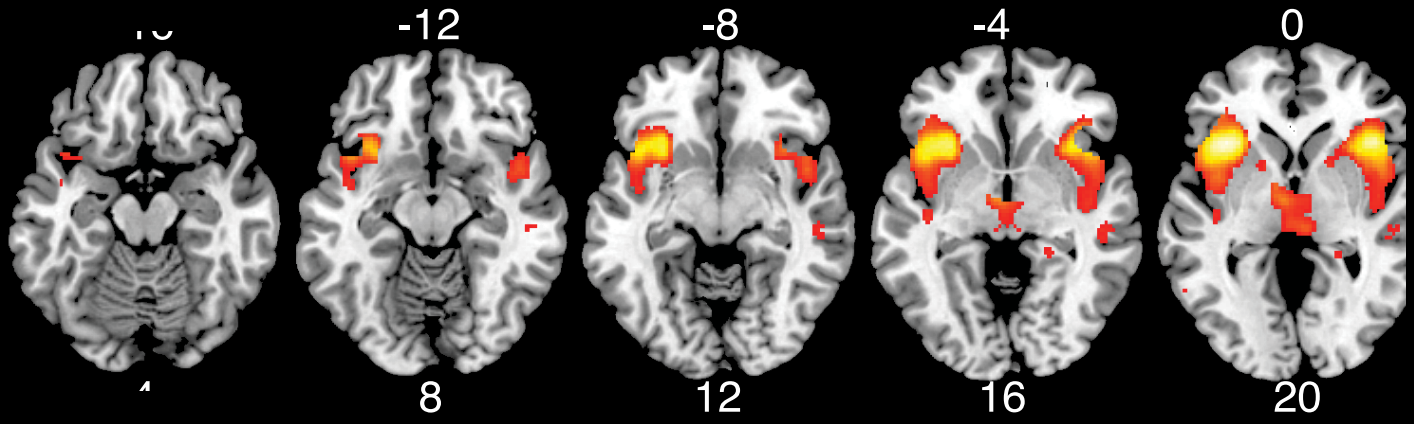


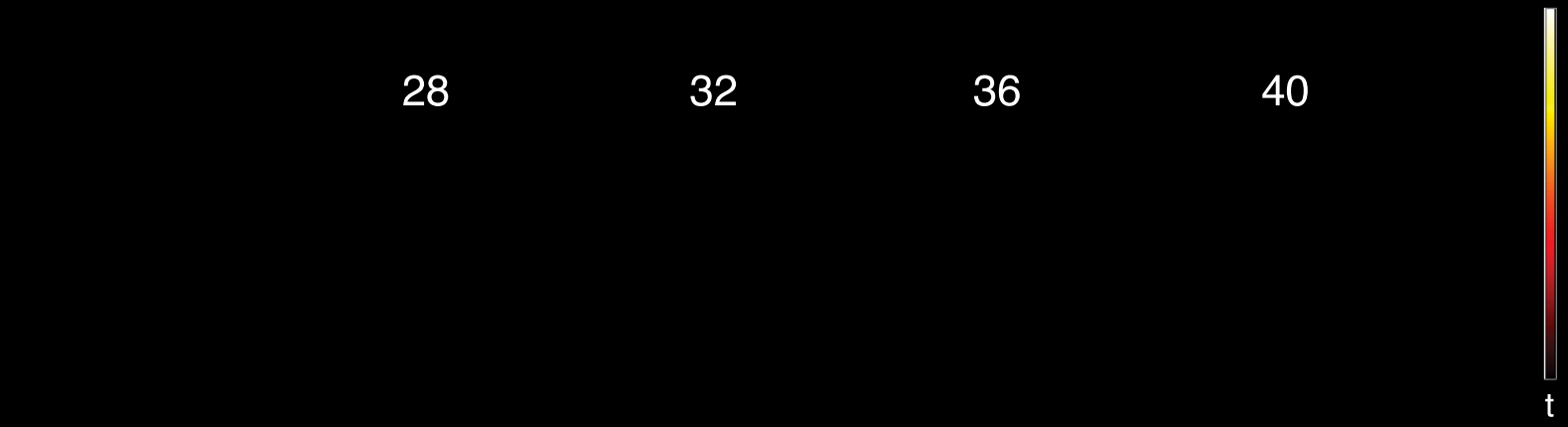
Powers, Mathys, Corlett (2017) *Science*



Powers, Mathys, Corlett (2017) *Science*

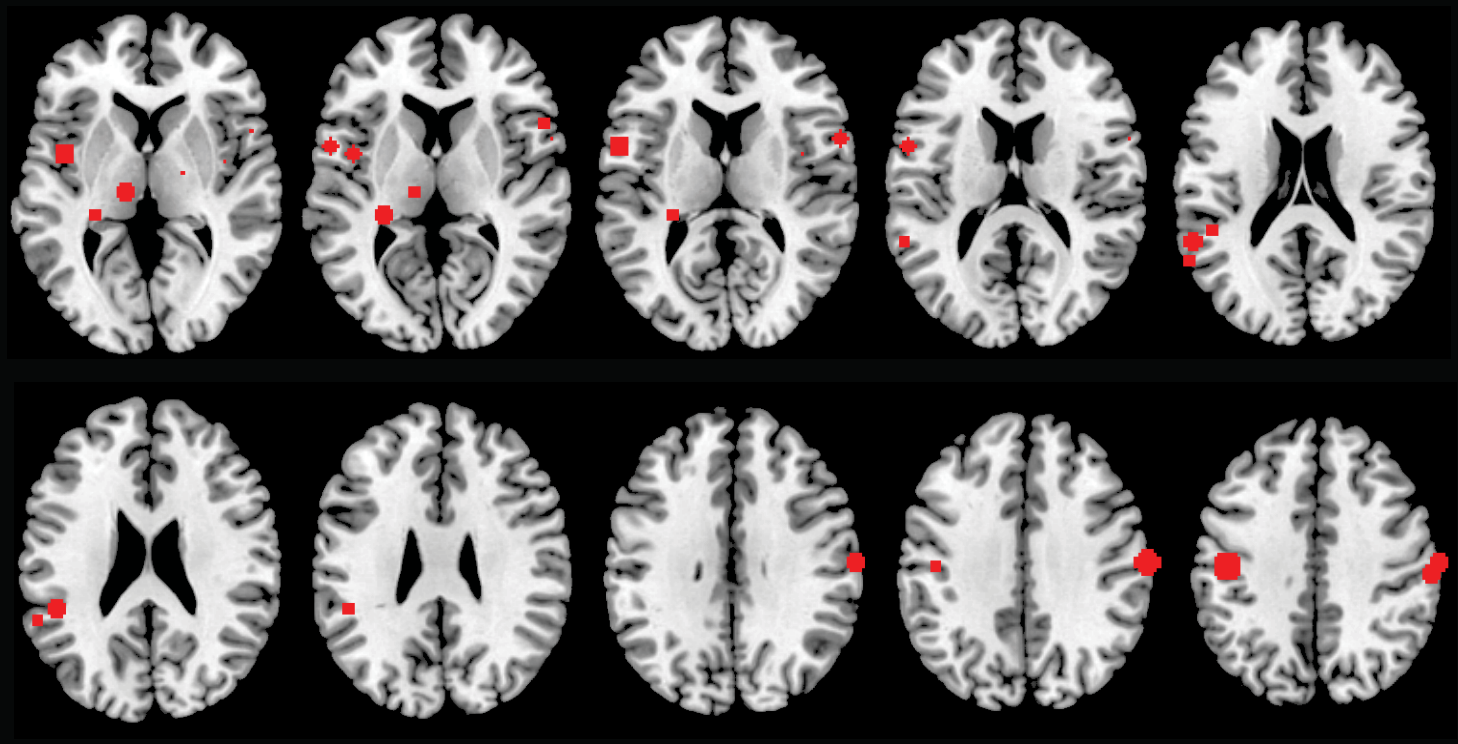
Whole-Brain Analysis: "Yes" vs "No" on No-Tone Trials





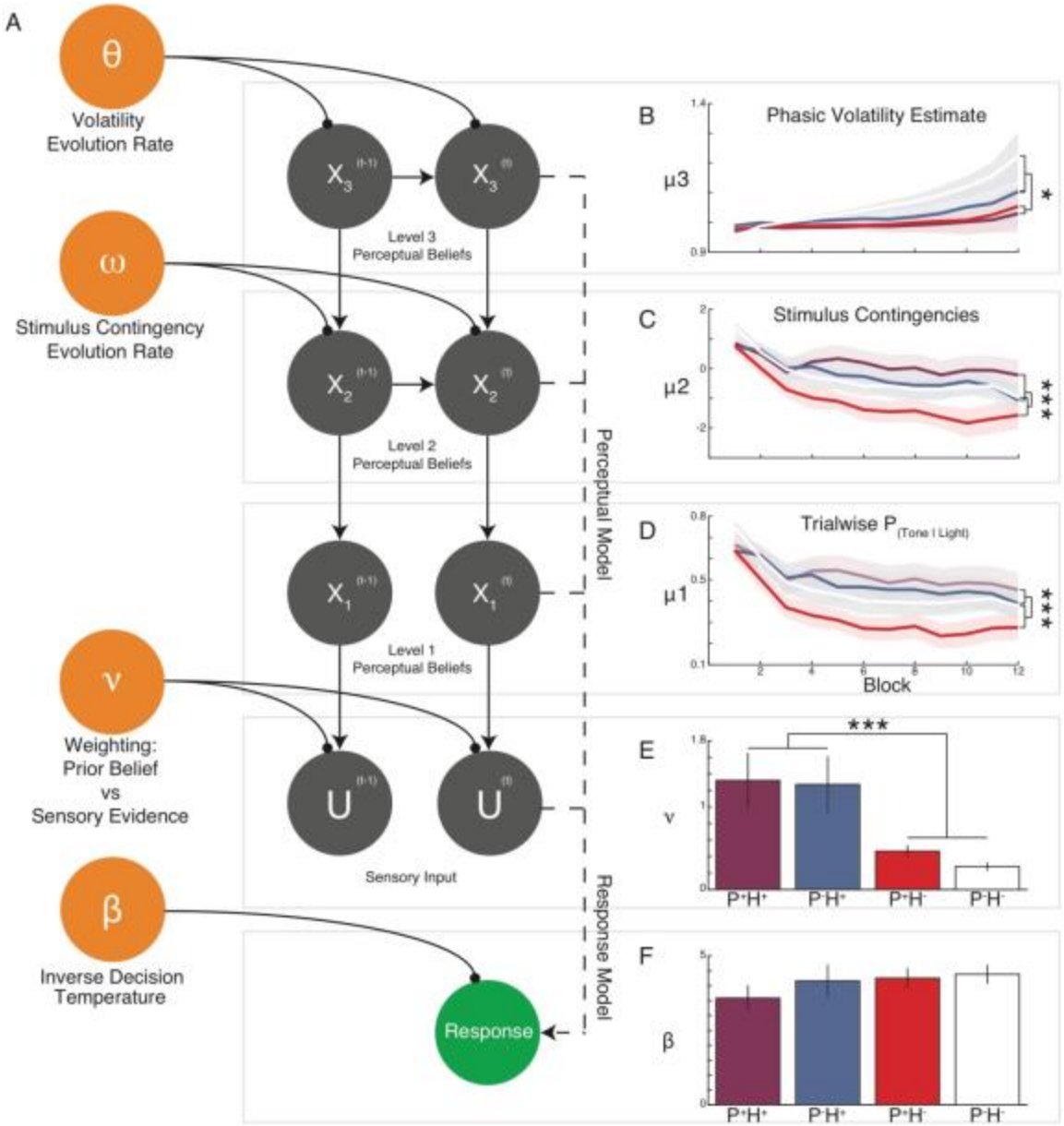
Powers, Mathys, Corlett (2017) *Science*

Regions Involved in Hallucinations: Symptom Capture



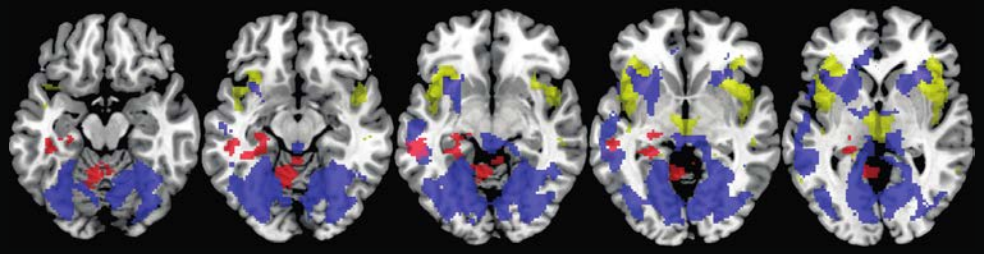
Jardri et al. (2011) *AJP*

Behavioral Measures of Perceptual Belief Differ Among Groups



Powers, Mathys, Corlett (2017) *Science*

Neural Correlates of Perceptual Belief Differ Among Groups



Powers, Mathys, Corlett (2017) *Science*

Conclusions

- Sensory conditioning is capable of producing hallucination-like phenomena.
- Participants who experience spontaneous hallucinations are more likely to report conditioned hallucinations.
- A network similar to that identified in symptom capture-based imaging studies of hallucinations is engaged during conditioned hallucinations and may be parsed based upon a computational model of perception
- On HGF analysis, parameters signifying perceptual belief weighting and belief volatility distinguished participants with hallucinations and psychosis, respectively.
- Dissection of the conditioned hallucinations network based upon belief trajectories identified regions subserving different computational functions that also differed across groups.

Future Directions

- Effective connectivity
- Pharmacological manipulations
- TMS
- Early diagnosis (pludrome)

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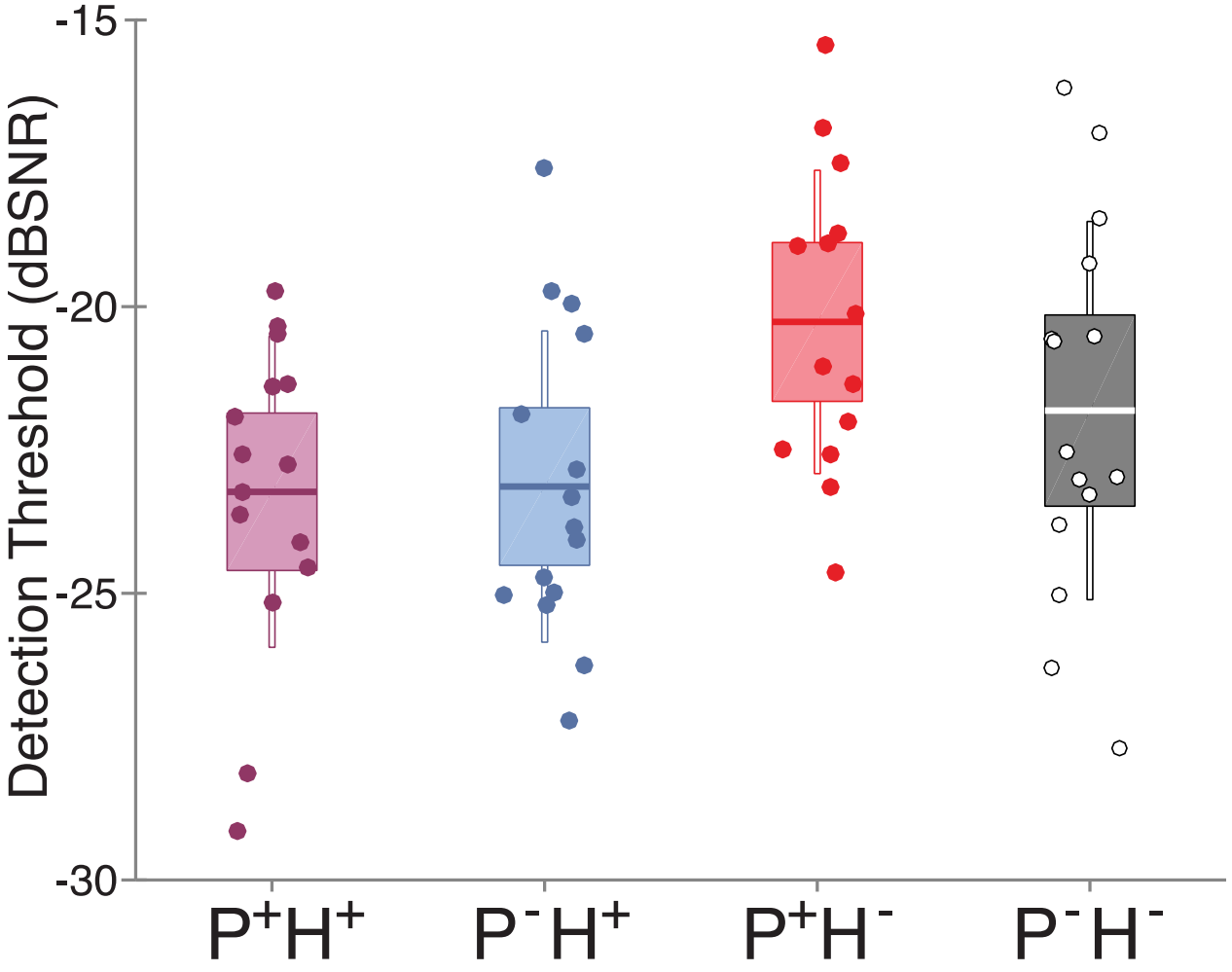
Threshold by Group



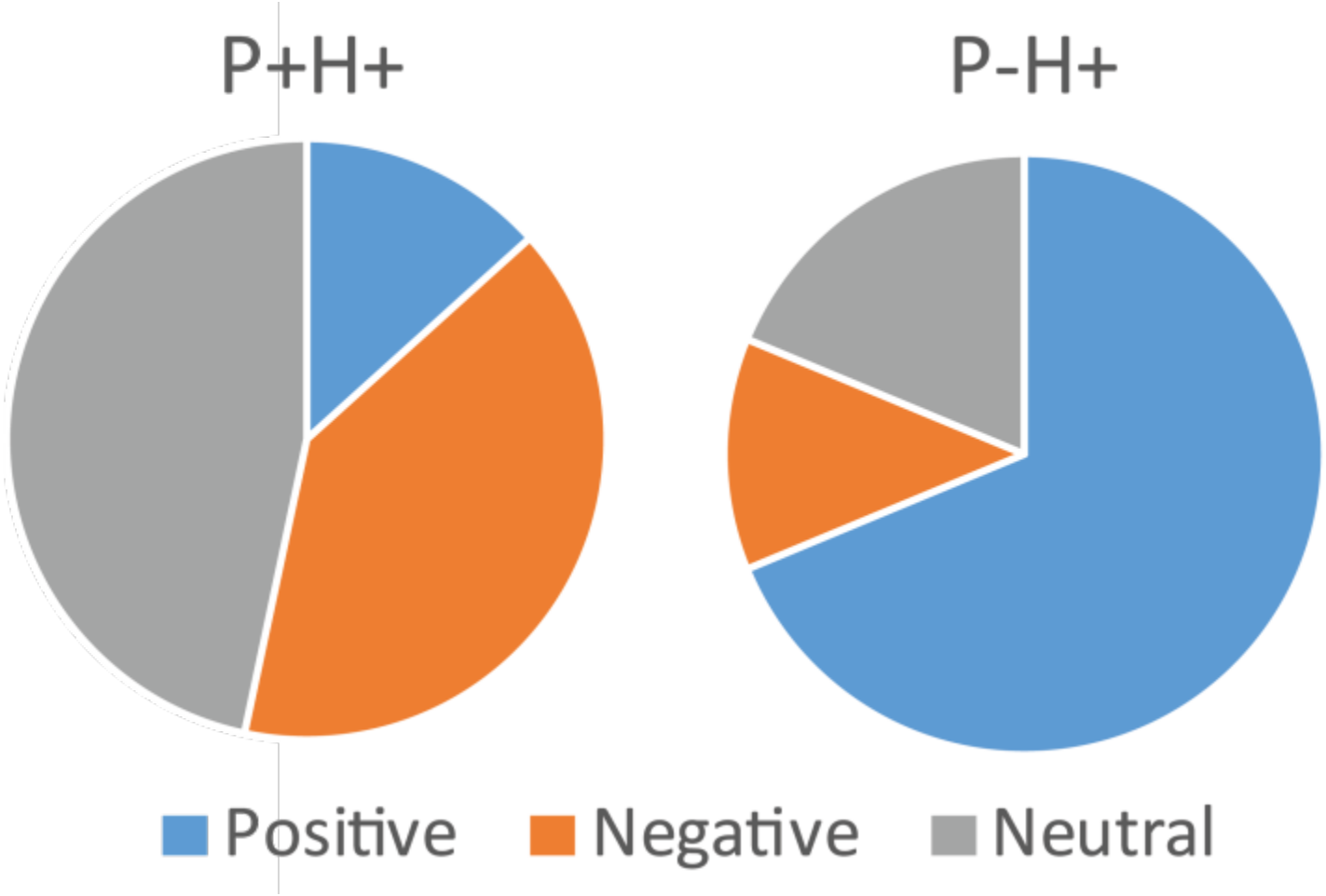
Powers, Mathys, Corlett (2017) *Science*

Phenomenological Comparison:

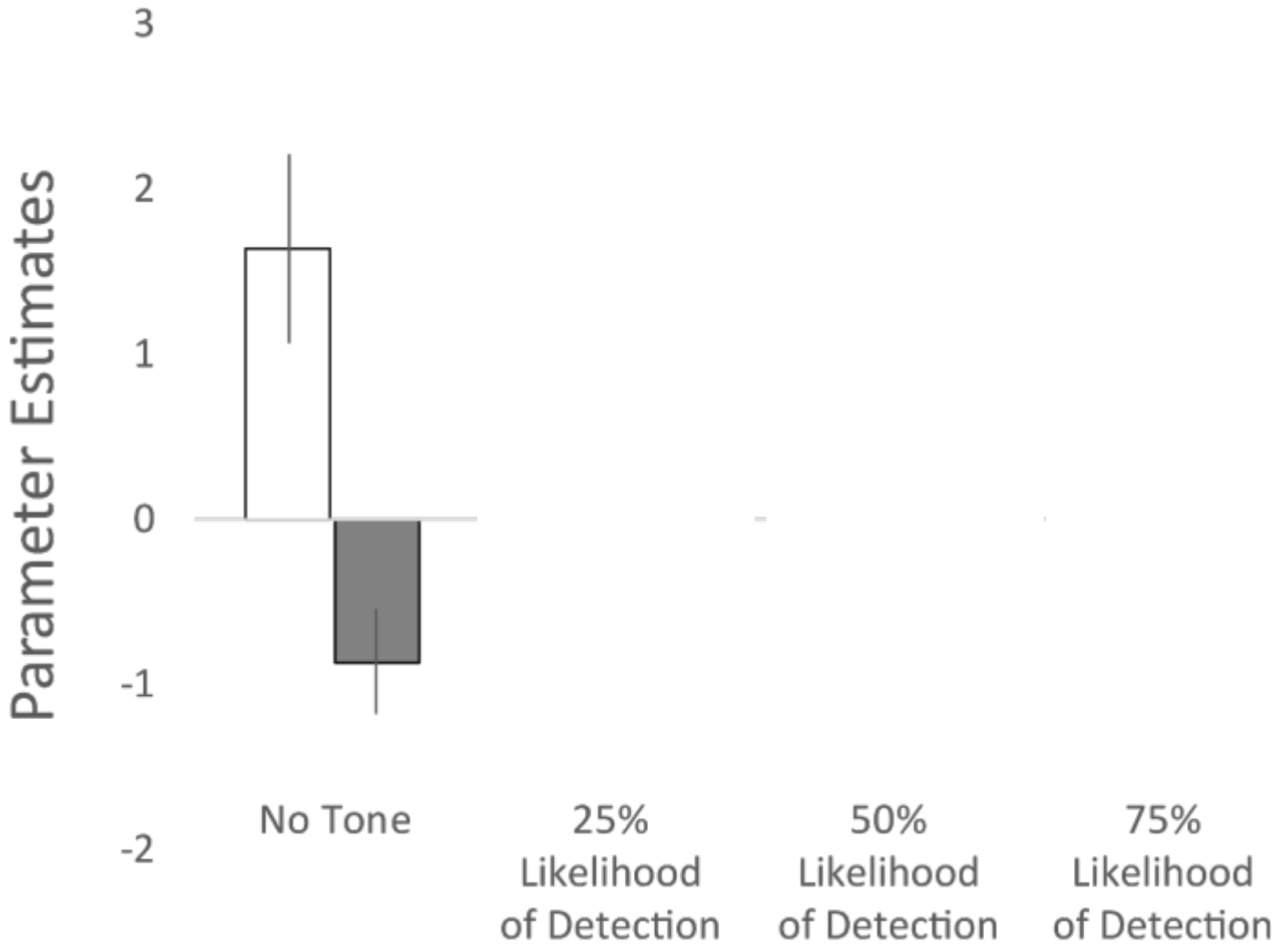
Formal Measures of Voice-Hearing

	P+H+ Mean ± SEM	P-H+ Mean ± SEM	p	p (corr)
Total AHRS Score	25 ± 1.09	22.78 ± 0.91	0.1277	ns
AHRS Score Frequency Item	**4.38 ± 0.81**	**1.65 ± 0.35**	**0.0036**	**0.0288**
AHRS Score Reality of Voices	4.44 ± 0.18	4.56 ± 0.16	0.6070	ns
AHRS Score Loudness of Voices	2.81 ± 0.25	3.12 ± 0.26	0.3966	ns
AHRS Score Number of Voices	4 ± 0.5	4.85 ± 0.39	0.1866	ns
AHRS Score Extent of Utterance	3.44 ± 0.29	2.82 ± 0.29	0.1419	ns
AHRS Score Influence of Voices	3.31 ± 0.37	4.65 ± 0.37	0.0169	ns
AHRS Score Distress Due to Voices	**2.63 ± 0.41**	**1 ± 0**	**0.0003**	**0.0024**
BAVQR Malevolence Score	**5.69 ± 1.29**	**0 ± 0**	**0.0001**	**0.0008**
BAVQR Benevolence Score	**4.06 ± 1.36**	**13.53 ± 0.69**	**0.0000**	**0.0000**
BAVQR Omnipotence Score	7.6 ± 1.12	4.71 ± 0.68	0.0315	ns
BAVQR Resistance Emotion Score	**6.14 ± 1.02**	**0.59 ± 0.41**	**0.0000**	**0.0001**
BAVQR Resistance Behavior Score	**8.93 ± 1.22**	**0.88 ± 0.4**	**0.0000**	**0.0000**
BAVQR Engagement Emotion Score	**1.67 ± 0.77**	**8.76 ± 0.54**	**0.0000**	**0.0000**
BAVQR Engagement Behavior Score	**2.53 ± 0.89**	**8.38 ± 0.69**	**0.0000**	**0.0002**
Age at First Voice	**22.93 ± 3.4**	**7.47 ± 1.35**	**0.0002**	**0.0016**

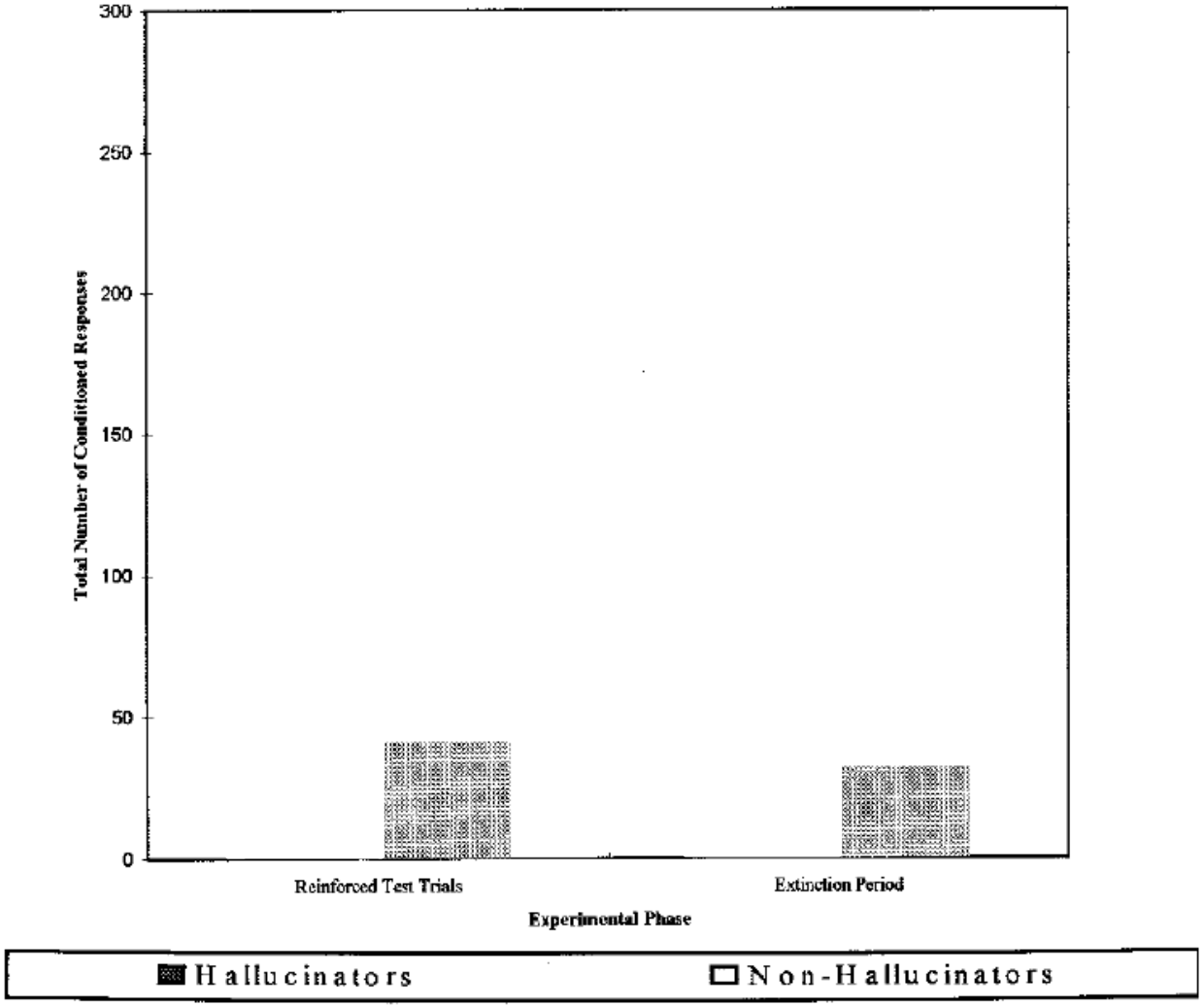
Experiences Divulging Voice-Hearing for the First Time



Auditory-responsive regions respond to hallucinated tones as if they were present



Those who hallucinate may be more susceptible to sensory conditioning



Kot & Serper 2002

Corlett & Fletcher, 2014

General Methods