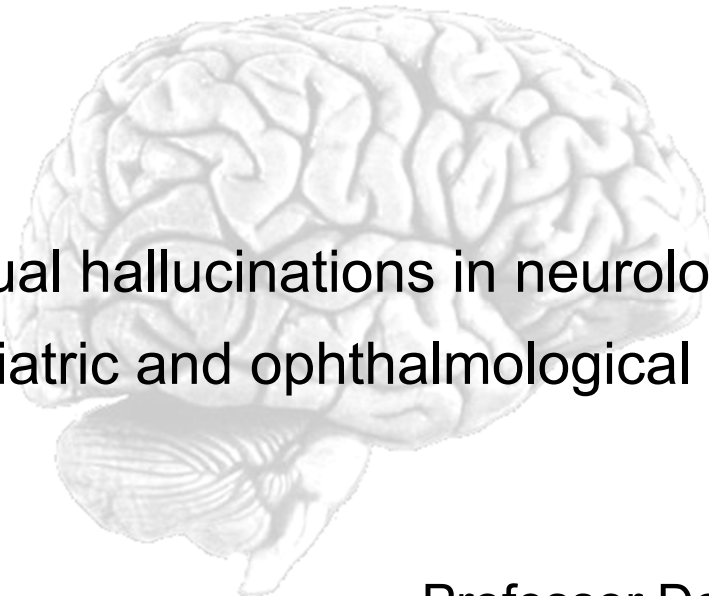




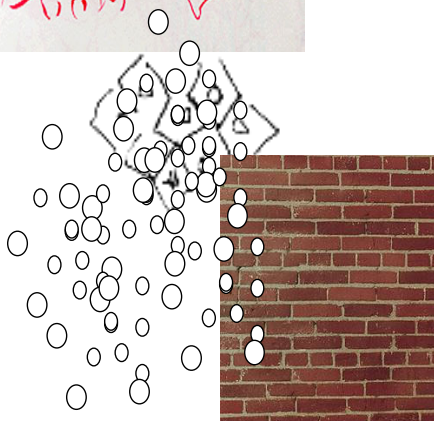
# Visual hallucinations in neurological, psychiatric and ophthalmological disease

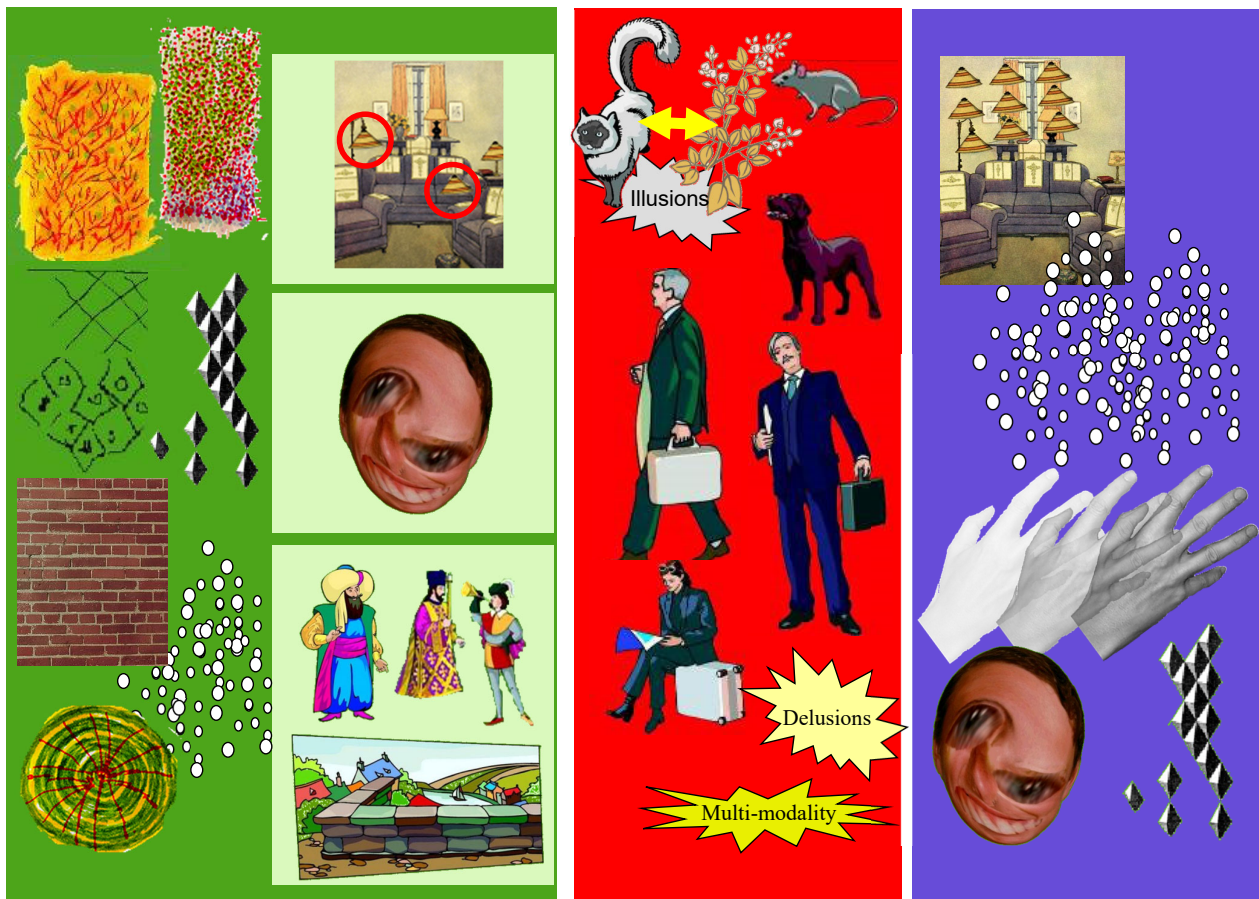
Professor Dominic ffytche

Institute of Psychiatry,  
Psychology and Neuroscience  
King's College London

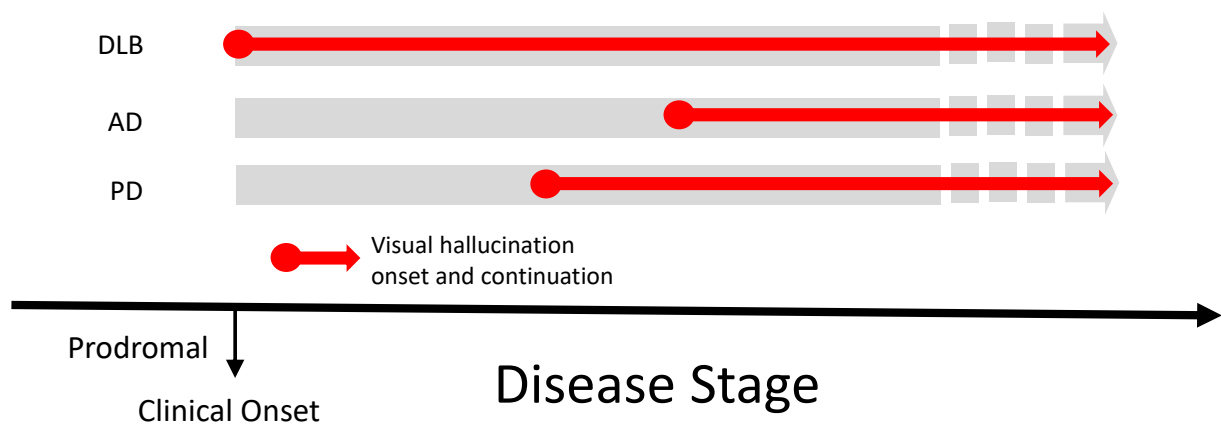
## Why study visual hallucinations?

- Important clinical symptom
- Biomarker for prognosis and outcome

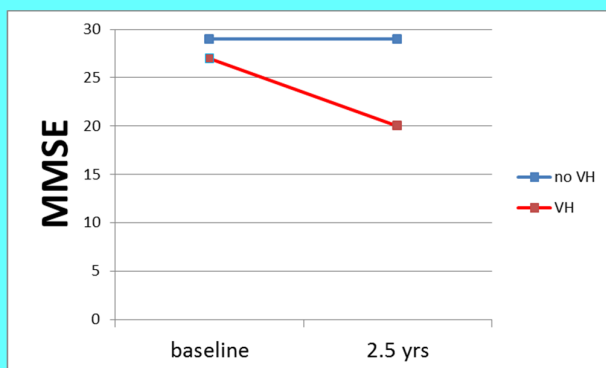




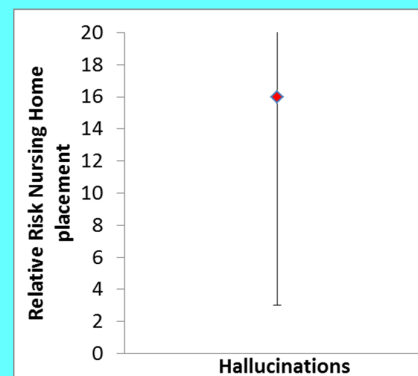
ffytche *Dialogues Clin Neurosci* 2007



PD

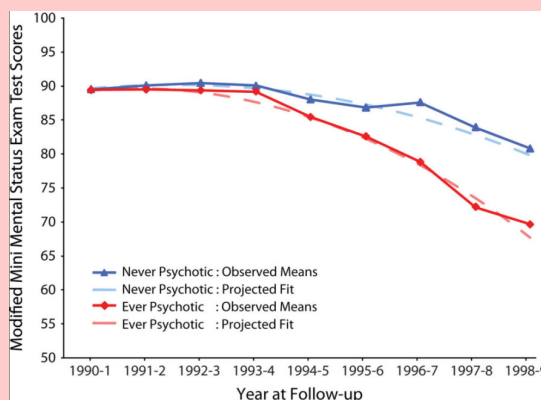


Ibarretxe-Bibao et al *JNNP* 2010

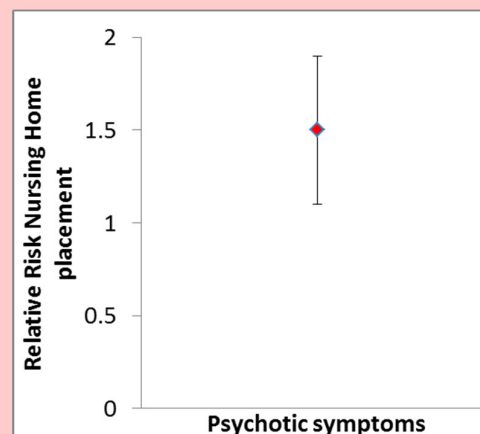


Goetz and Stebbins *Neurology* 1993

AD

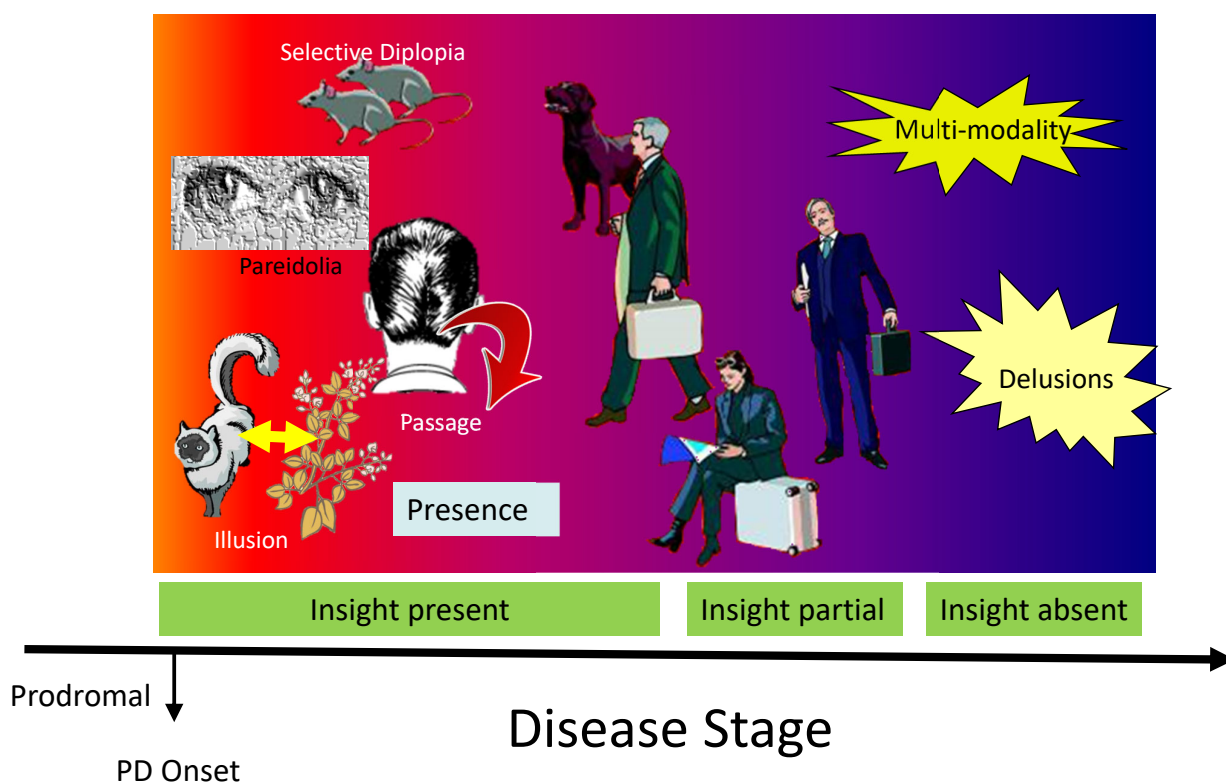


Emanuel et al *Am J Ger Psychiatry* 2011



Stern et al *JAMA* 1997

## PD Psychosis



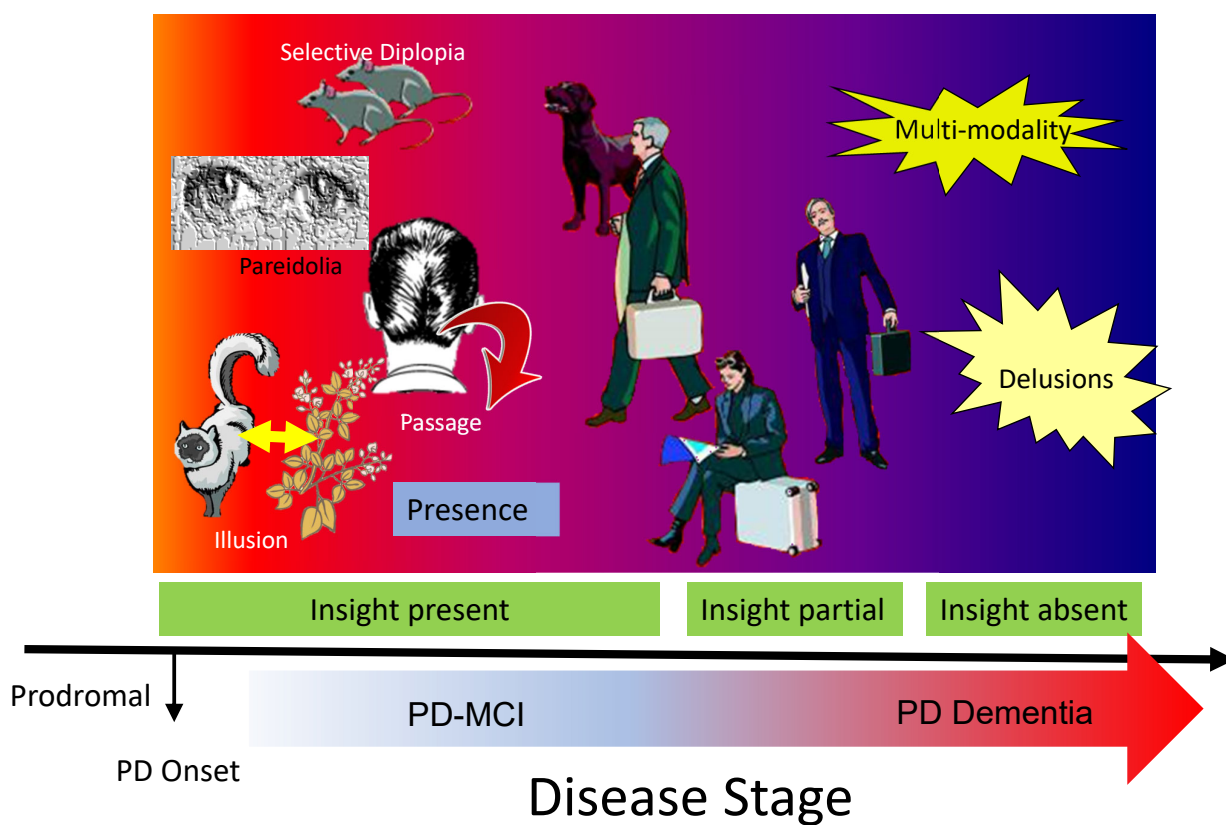


Pareidolia

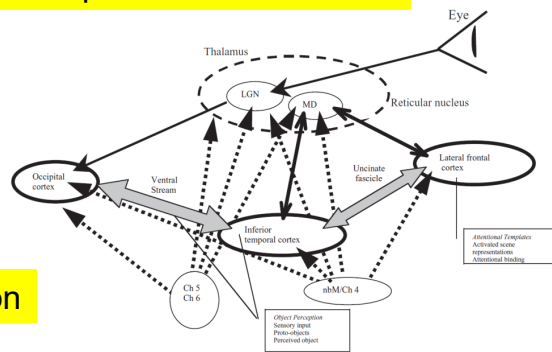


Ebersbach *Mov Disord* 2003

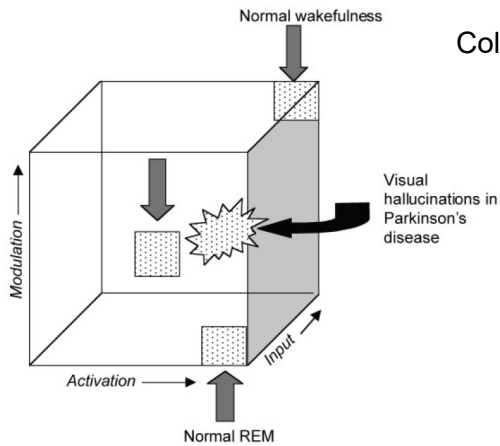
## PD Psychosis



## Perception Attention Deficit

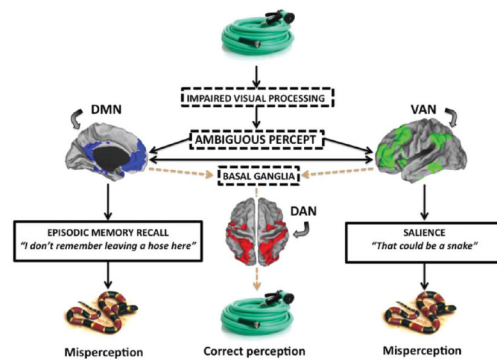


## Activation-Input-Modulation



Collerton et al *Behav Brain Sci* 2005

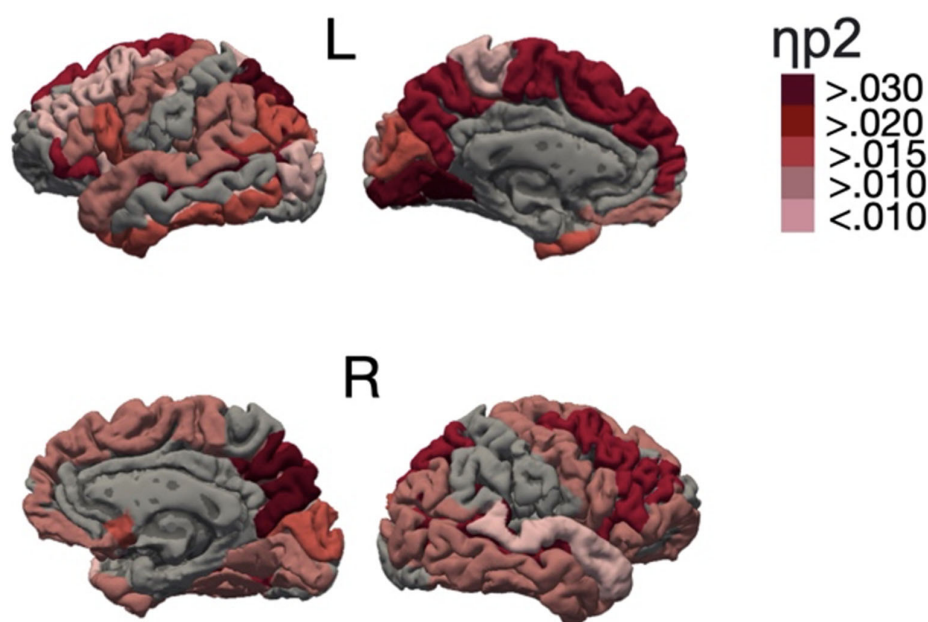
## Attentional Control



Shine et al *Mov Dis* 2011

| Domain             |                | Parkinson's disease<br>(PD-MCI) | Parkinson's disease<br>(MMSE > 25) |
|--------------------|----------------|---------------------------------|------------------------------------|
| Visual perception  | Object         | ✓                               | ✓                                  |
|                    | Face           | ✓                               |                                    |
|                    | Spatial        | ✓                               |                                    |
| Executive function | Stroop         | ✓                               | ✓                                  |
|                    | Go/NoGO        | ✓                               | ✓                                  |
|                    | Verbal fluency | ✓                               | ✓                                  |
| Attention          |                | ✓                               |                                    |
| Memory             | Visual         | ✓                               | ✓                                  |
|                    | Verbal         | ✓                               |                                    |

# Cortical thickness



493 participants 135 PD-VH 358 PD-noVH

Vignando et al *Submitted*

Progress in Neurobiology 95 (2011) 629–635



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Progress in Neurobiology

journal homepage: [www.elsevier.com/locate/pneurobio](http://www.elsevier.com/locate/pneurobio)



## The Parkinson Progression Marker Initiative (PPMI)

Kenneth Marek, Danna Jennings, Shirley Lasch, Andrew Siderowf, Caroline Tanner, Tanya Simuni, Chris Coffey, Karl Kieburtz, Emily Flagg, Sohini Chowdhury, Werner Poewe, Brit Mollenhauer, Paracelsus-Elena Klinik, Todd Sherer, Mark Frasier, Claire Meunier, Alice Rudolph, Cindy Casaceli, John Seibyl, Susan Mendick, Norbert Schuff, Ying Zhang, Arthur Toga, Karen Crawford, Alison Ansbach, Pasquale De Blasio, Michele Piovella, John Trojanowski, Les Shaw, Andrew Singleton, Keith Hawkins, Jamie Eberling, Deborah Brooks, David Russell, Laura Leary, Stewart Factor, Barbara Sommerfeld, Penelope Hogarth, Emily Pighetti, Karen Williams, David Standaert, Stephanie Guthrie, Robert Hauser, Holly Delgado, Joseph Jankovic, Christine Hunter, Matthew Stern, Baochan Tran, Jim Leverenz, Marne Baca, Sam Frank, Cathi-Ann Thomas, Irene Richard, Cheryl Deeley, Linda Rees, Fabienne Sprenger, Elisabeth Lang, Holly Shill, Sanja Obradov, Hubert Fernandez, Adrienna Winters, Daniela Berg, Katharina Gauss, Douglas Galasko, Deborah Fontaine, Zoltan Mari, Melissa Gerstenhaber, David Brooks, Sophie Malloy, Paolo Barone, Katia Longo, Tom Comery, Bernard Ravina, Igor Grachev, Kim Gallagher, Michelle Collins, Katherine L. Widnell, Suzanne Ostrowizki, Paulo Fontoura, Tony Ho, Johan Luthman, Marcel van der Brug, Alastair D. Reith, Peggy Taylor

The Parkinson Progression Marker Initiative<sup>1</sup>

### ARTICLE INFO

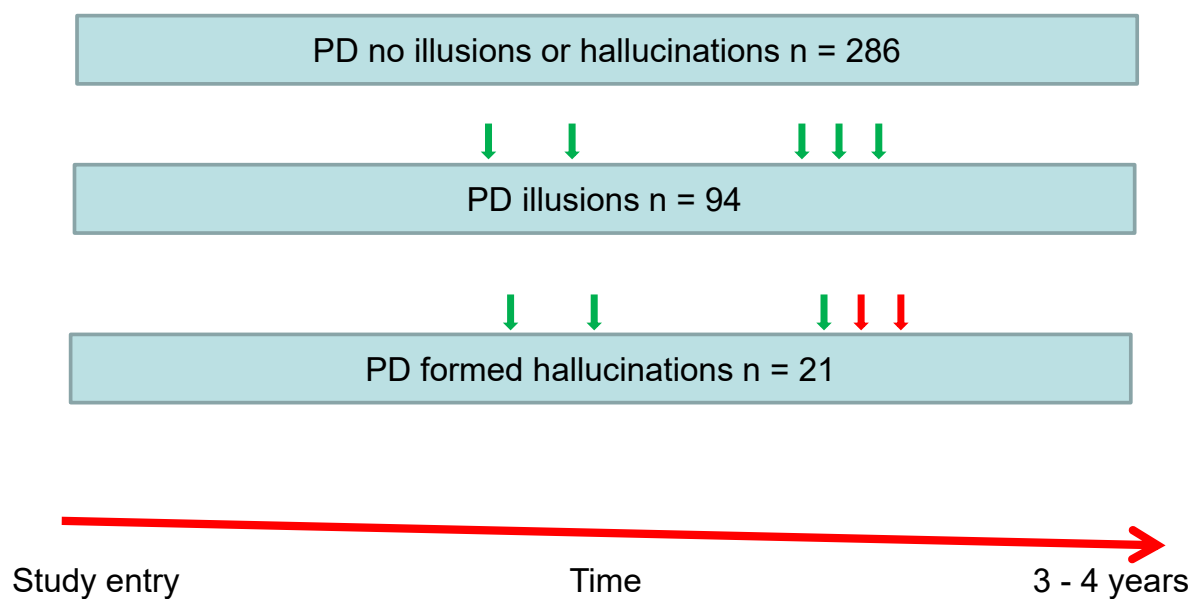
Article history:  
Available online 14 September 2011

Keywords:  
biomarker  
Dopamine transporter imaging  
Diffusion tensor imaging  
cerebrospinal fluid  
alpha synuclein

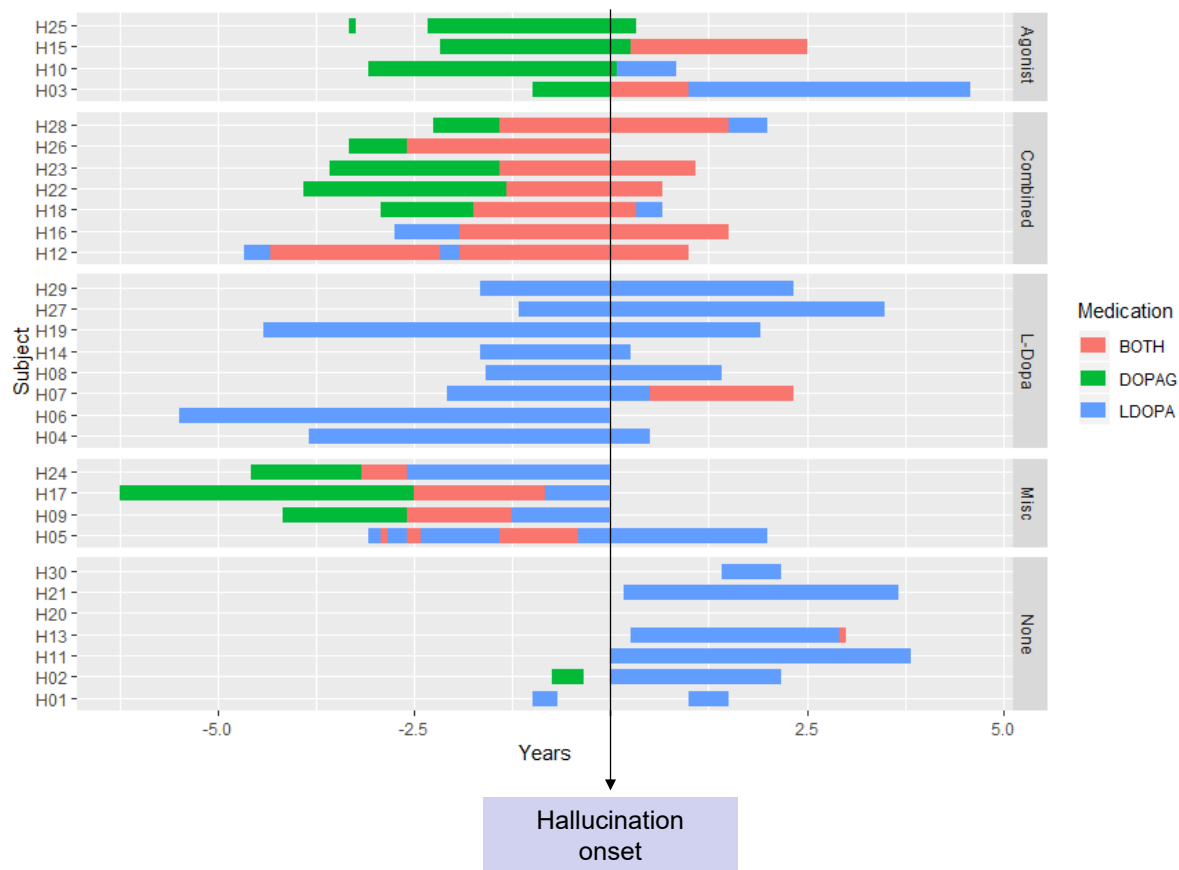
### ABSTRACT

The Parkinson Progression Marker Initiative (PPMI) is a comprehensive observational, international, multi-center study designed to identify PD progression biomarkers both to improve understanding of disease etiology and course and to provide crucial tools to enhance the likelihood of success of PD modifying therapeutic trials. The PPMI cohort will comprise 400 recently diagnosed PD and 200 healthy subjects followed longitudinally for clinical, imaging and biospecimen biomarker assessment using standardized data acquisition protocols at twenty-one clinical sites. All study data will be integrated in the PPMI study database and will be rapidly and publicly available through the PPMI web site: [www.ppmi-info.org](http://www.ppmi-info.org). Biological samples including longitudinal collection of blood, cerebrospinal fluid (CSF) and urine will be available to scientists by application to an independent PPMI biospecimen review committee also through the PPMI web site. PPMI will rely on a partnership of government, PD foundations, industry and academics working cooperatively. This approach is crucial to enhance the potential for success of this ambitious strategy to develop PD progression biomarkers that will accelerate research in disease modifying therapeutics.

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ffytche et al *JNNP* 2017



Dave et al *Mov Dis Clin Pract* 2020

## PPMI baseline data

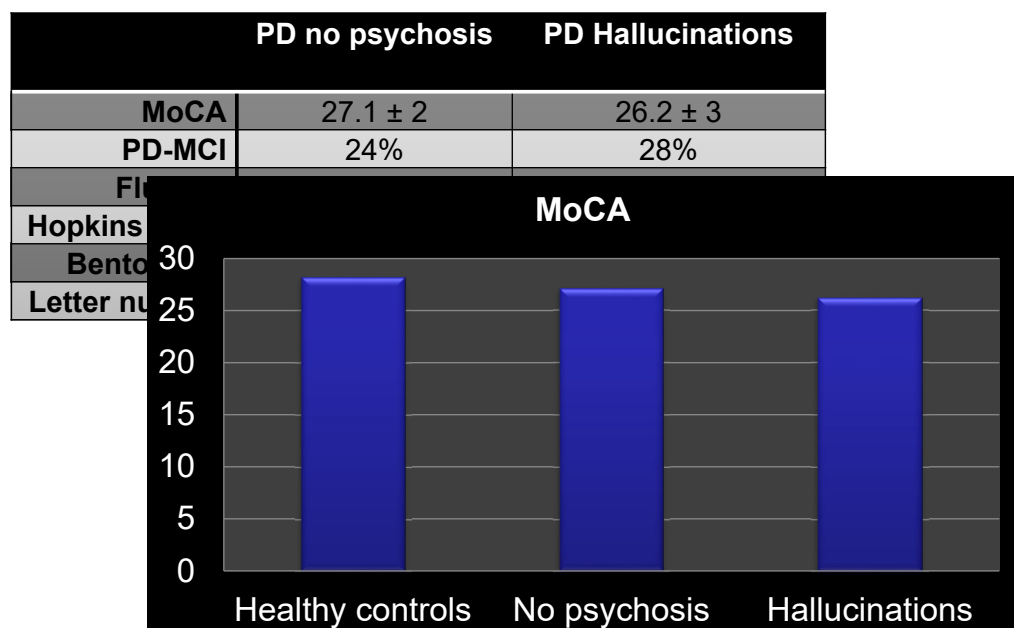
### Study entry

|                       | PD no psychosis | PD Hallucinations |
|-----------------------|-----------------|-------------------|
| Age                   | 61.9 ± 9 yrs    | 64.4 ± 7 yrs      |
| Gender                | Male = 67%      | Male = 71%        |
|                       |                 |                   |
| PD Duration           | 6.5 ± 6 months  | 8.5 ± 7 months    |
| UPDRS part 111        | 21.1 ± 8        | 21.9 ± 7          |
| Tremor onset          | 79 %            | 76 %              |
| Bradykinesia onset    | 81 %            | 85 %              |
| Rigidity onset        | 77 %            | 76 %              |
| Postural onset        | 7 %             | 9%                |
| Left /symmetric onset | 43 %            | 47 %              |
|                       |                 |                   |

ffytche et al *JNNP* 2017

## PPMI baseline data

### Study entry

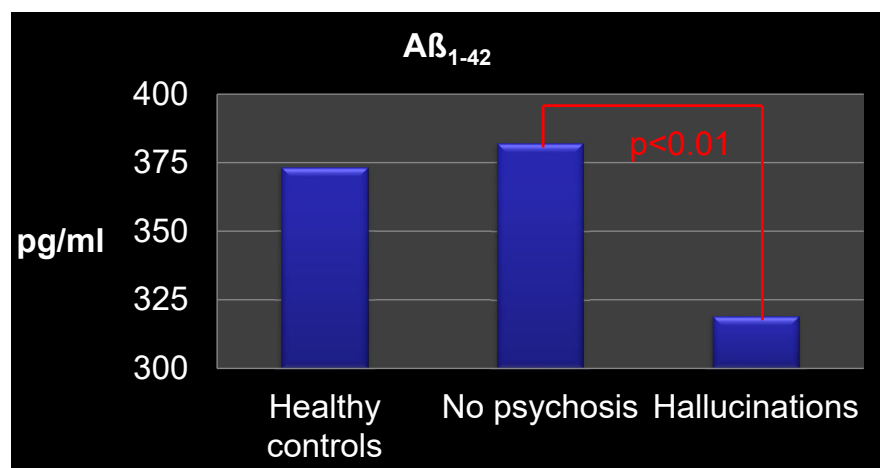


ffytche et al *JNNP* 2017

## PPMI baseline data

### Study entry

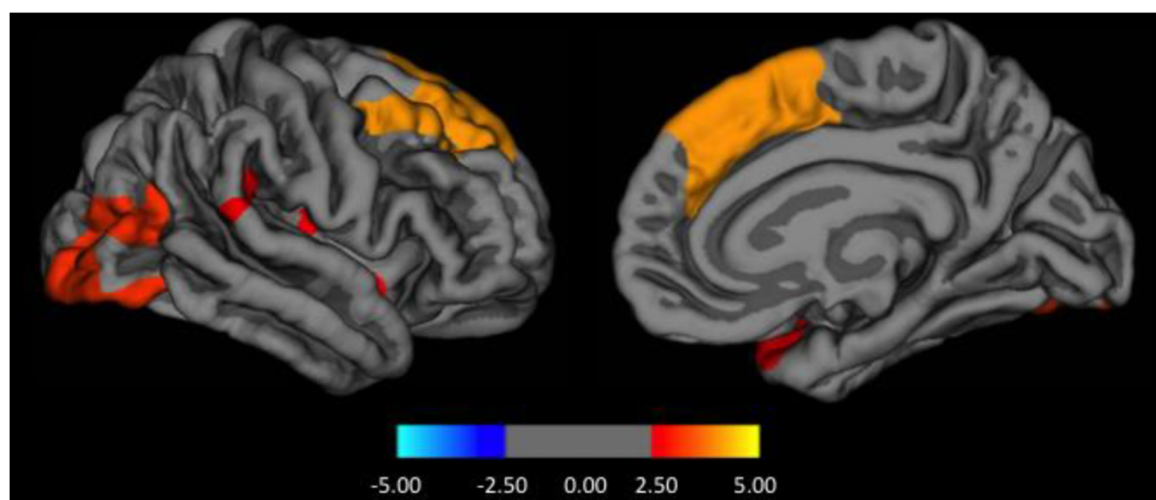
|                                           |       | PD no psychosis | PD Hallucinations |
|-------------------------------------------|-------|-----------------|-------------------|
| <b>A<math>\beta</math><sub>1-42</sub></b> | pg/ml | 382 $\pm$ 98    | 319 $\pm$ 115     |
| <b>Total-Tau</b>                          | pg/ml | 44.8 $\pm$ 17   | 49 $\pm$ 22       |
| <b>p-tau181</b>                           | pg/ml | 16.0 $\pm$ 10   | 16.3 $\pm$ 7      |
| <b><math>\alpha</math>-synuclein</b>      | pg/ml | 1884 $\pm$ 786  | 1969 $\pm$        |



ffytche et al *JNNP* 2017

## PPMI baseline data

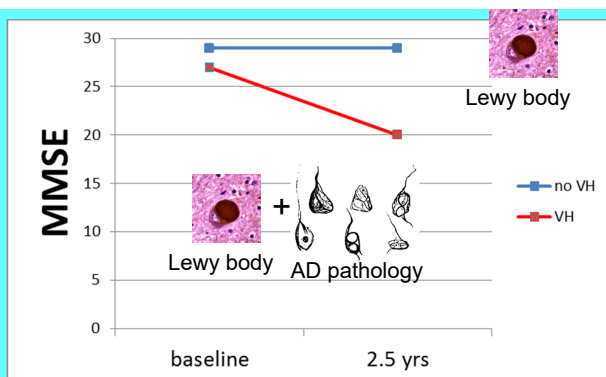
### Study entry



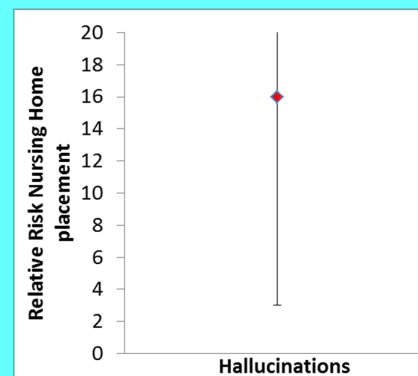
Cortical atrophy Hallucinations versus No psychosis

ffytche et al *JNNP* 2017

PD

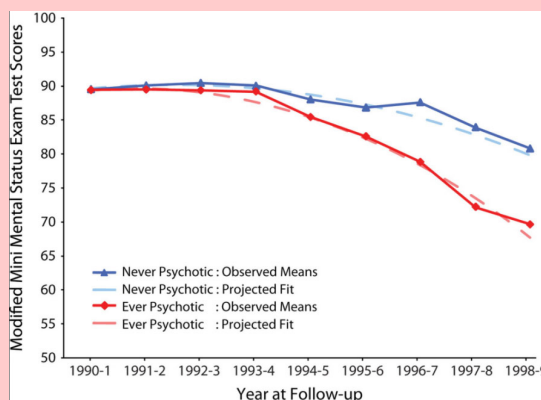


Ibarretxe-Bibao et al *JNNP* 2010

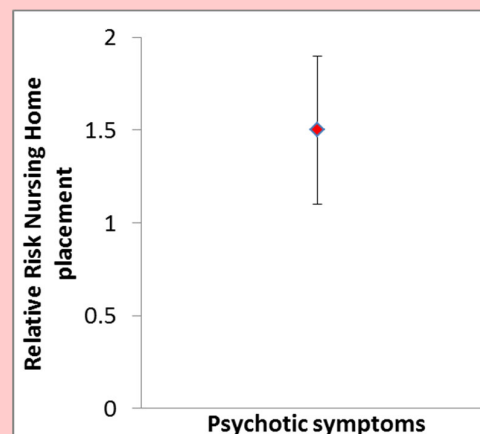


Goetz and Stebbins *Neurology* 1993

AD

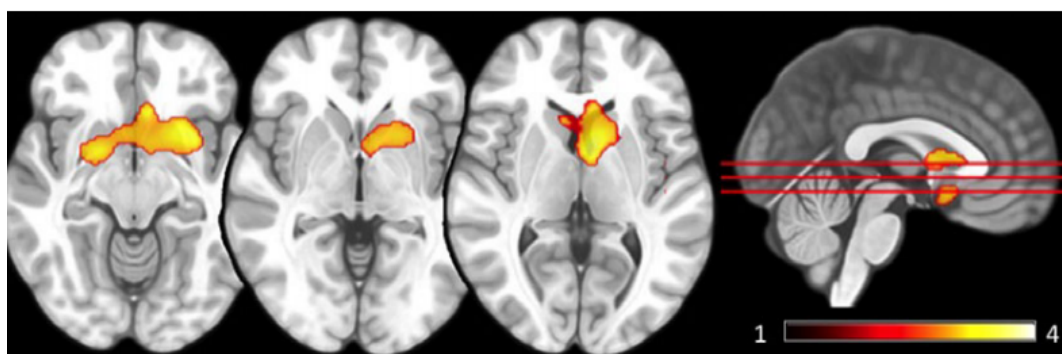


Emanuel et al *Am J Ger Psychiatry* 2011



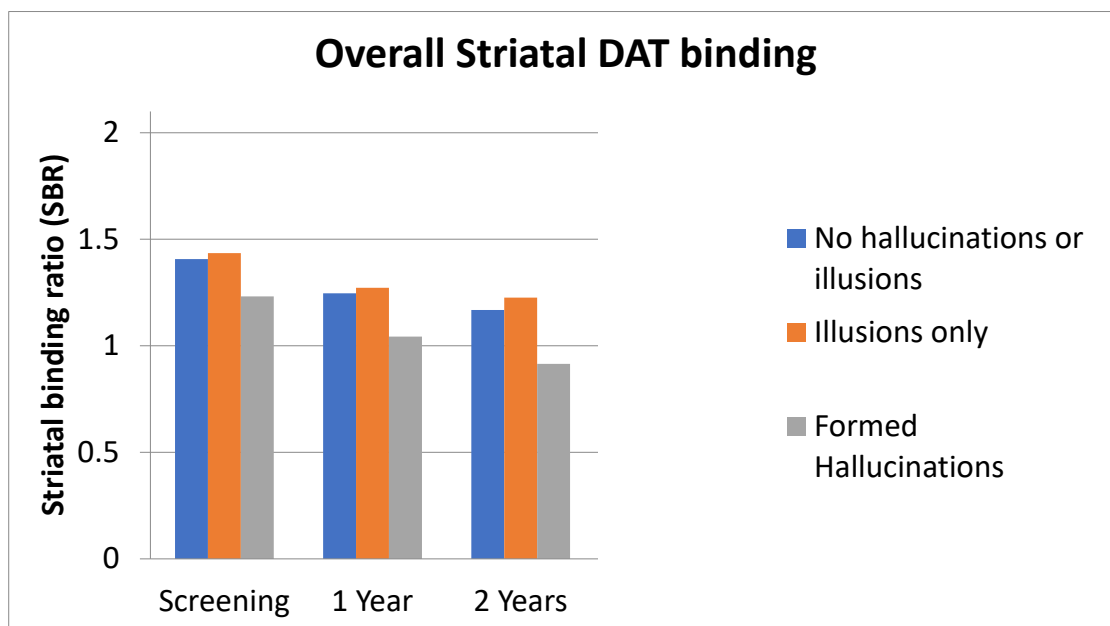
Stern et al *JAMA* 1997

## PD Psychosis Dopamine

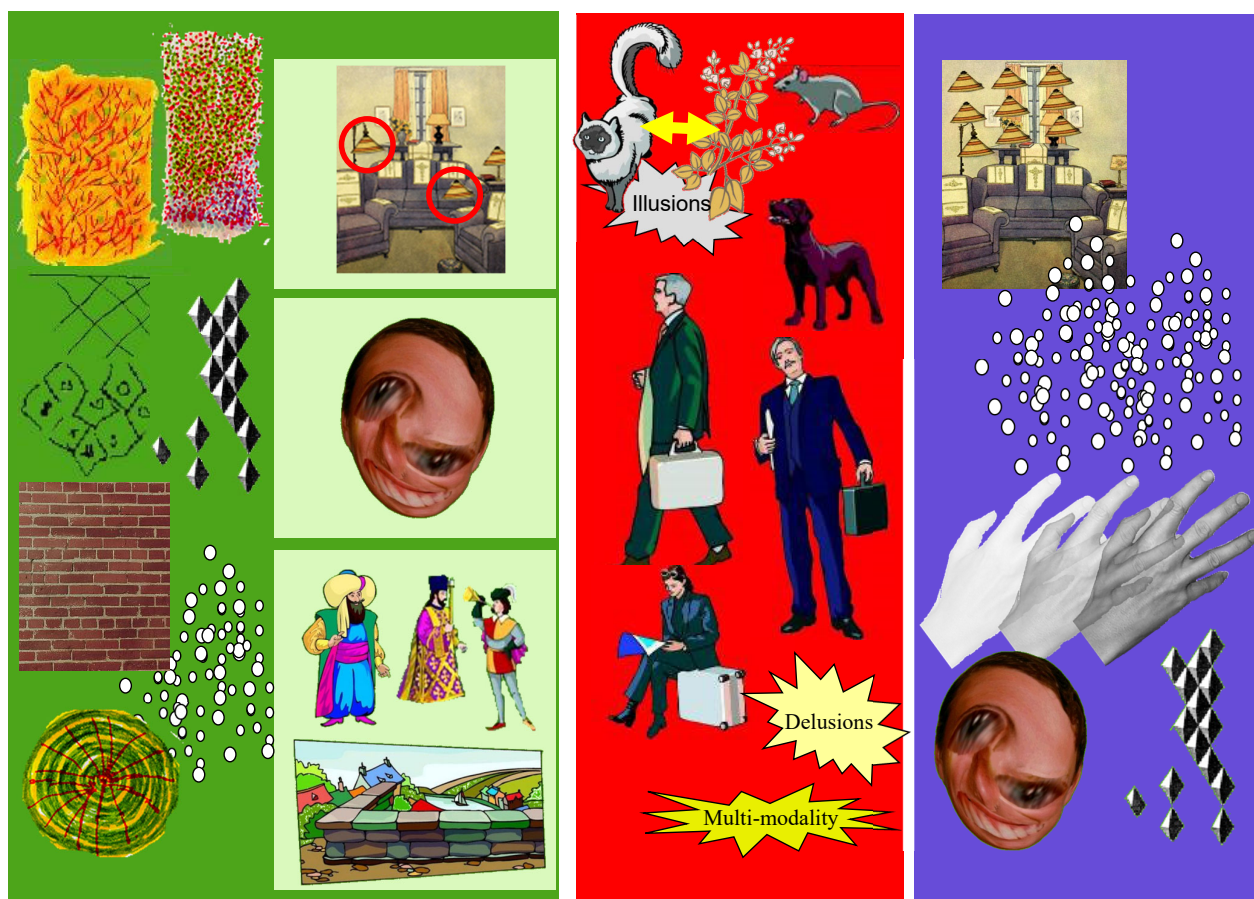


Reduced DAT binding in PD psychosis

Jaakkola et al *Eur J Neurol* 2017

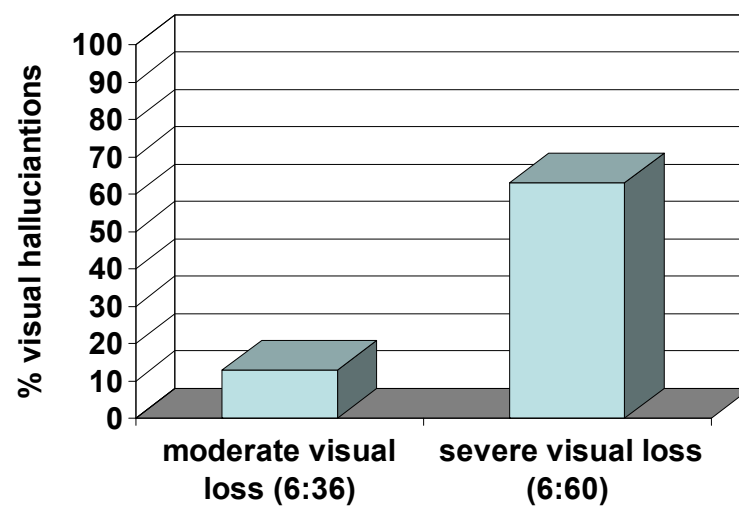


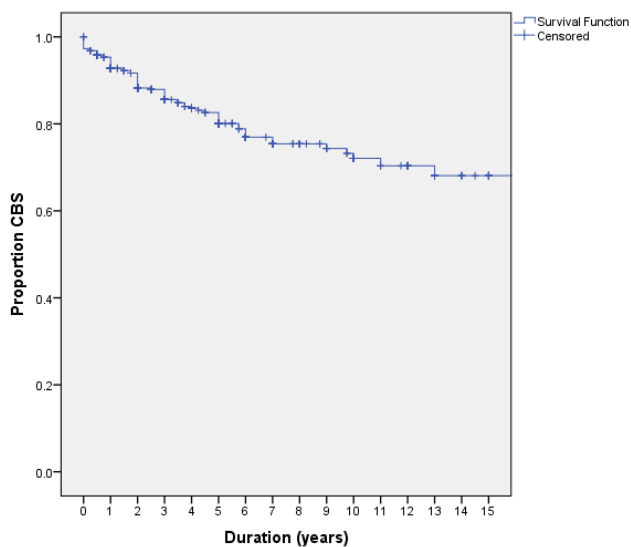
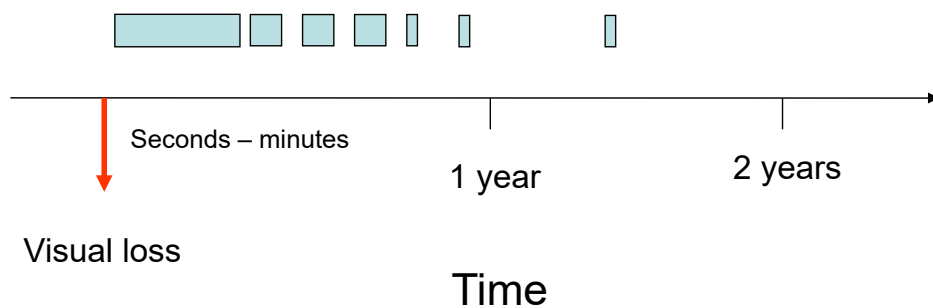
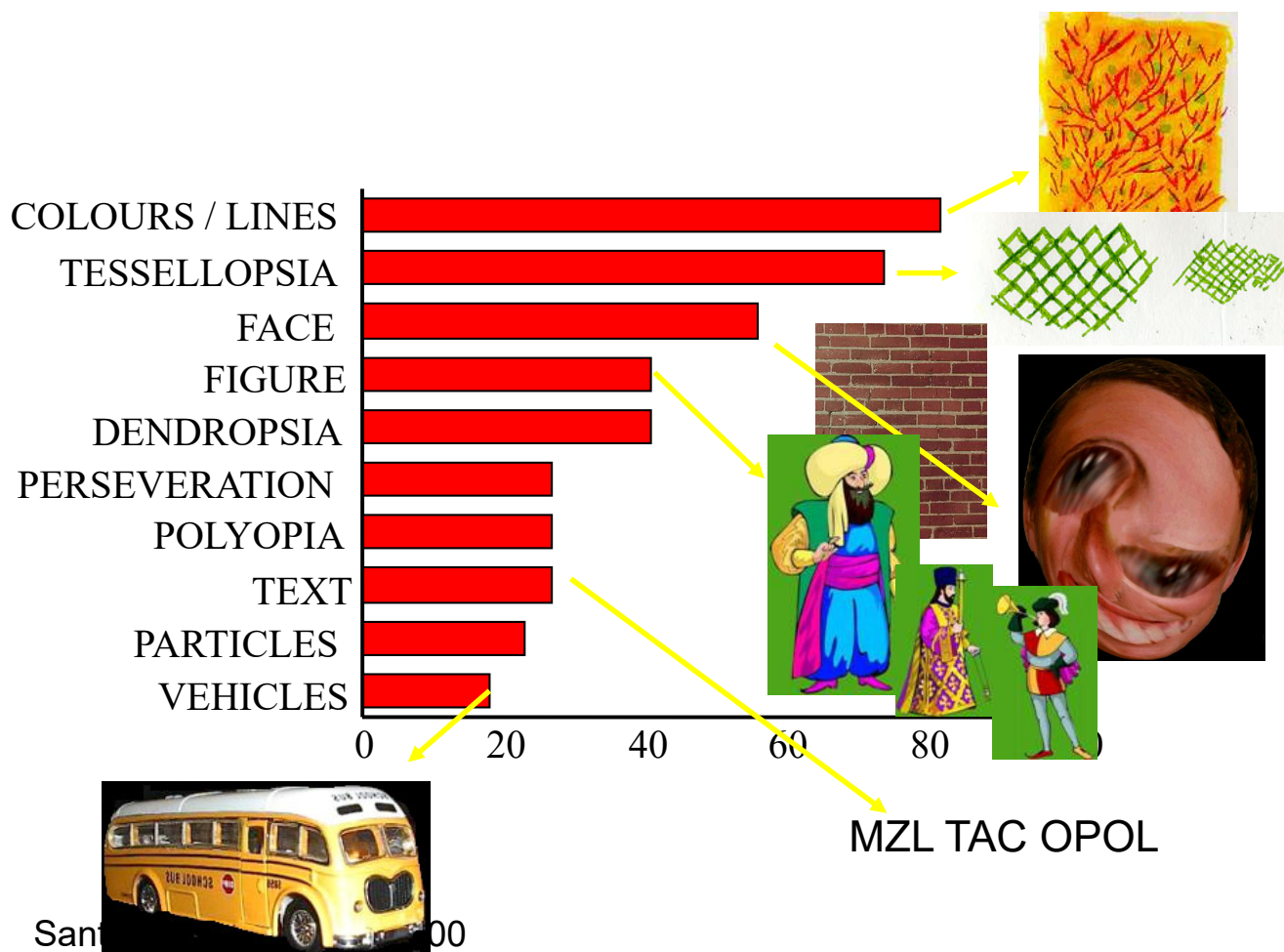
Dave et al *Mov Dis Clin Pract* 2020

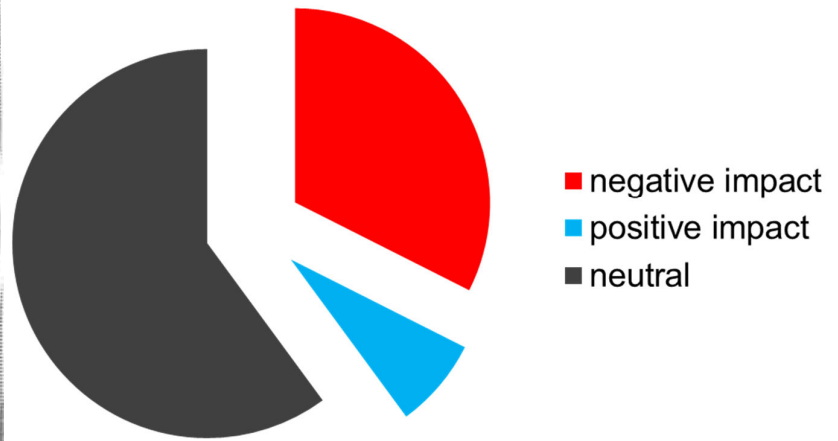




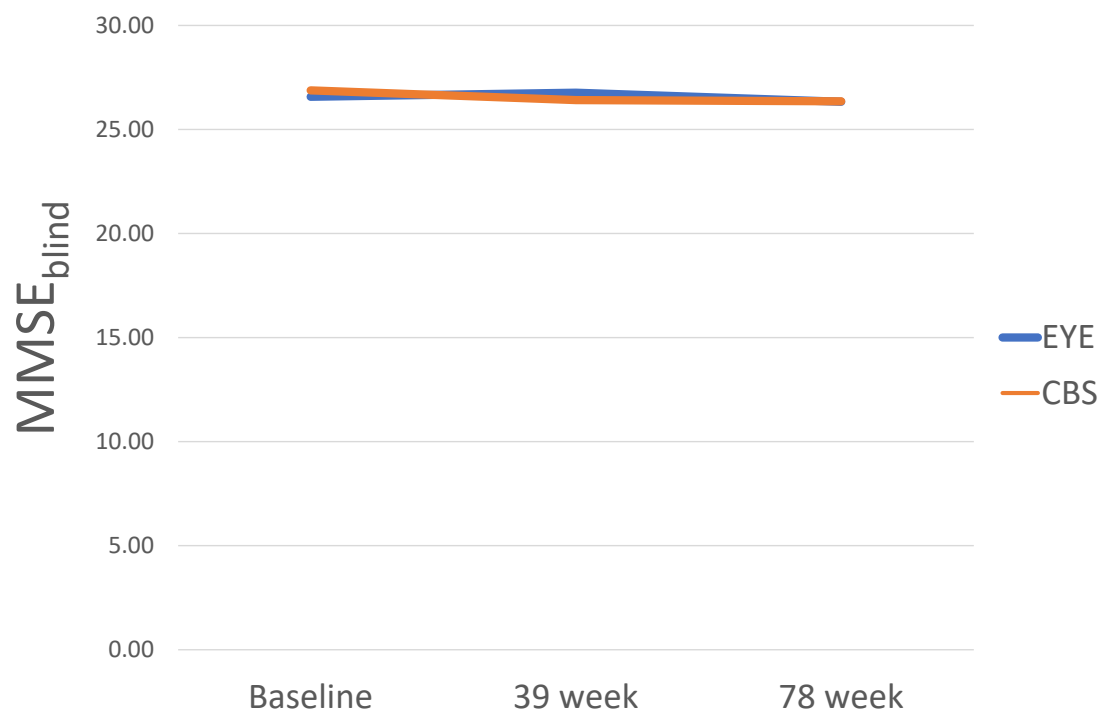
Charles Bonnet  
1720-1793



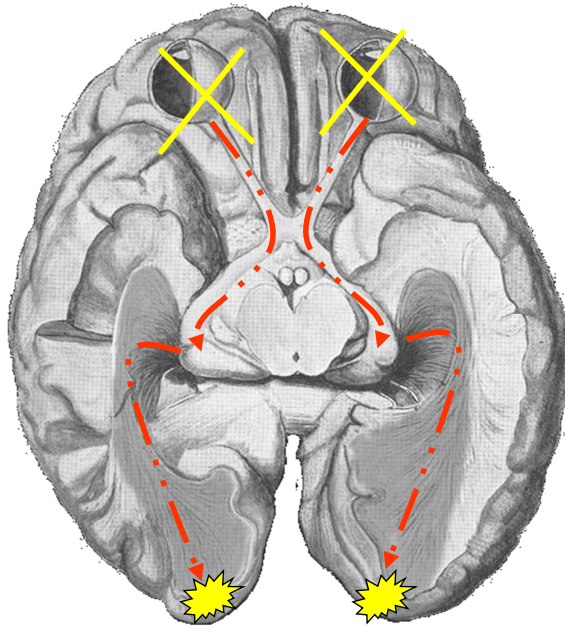




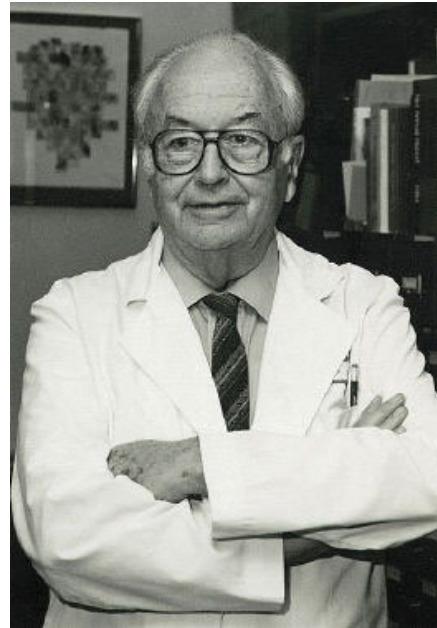
Cox and ffytche BJOPhth 2014



## Release / de-afferentation theory

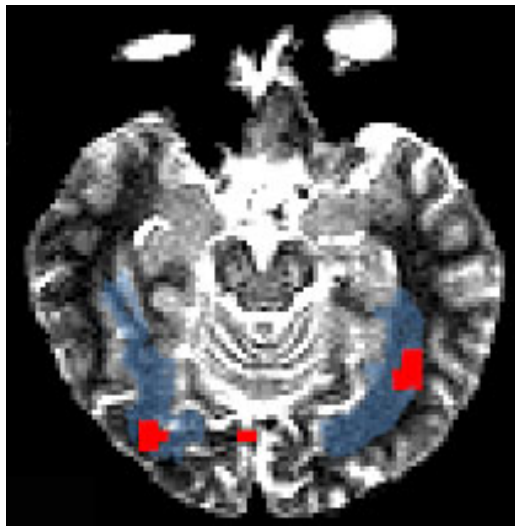


- Spontaneous activation
- Hyper-sensitivity

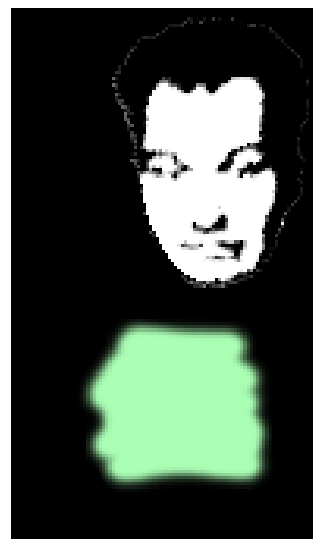
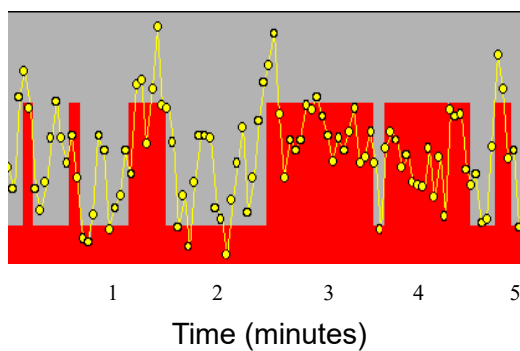


David Cogan  
1908-1993

*Cogan Graefe's Archive, 1973*

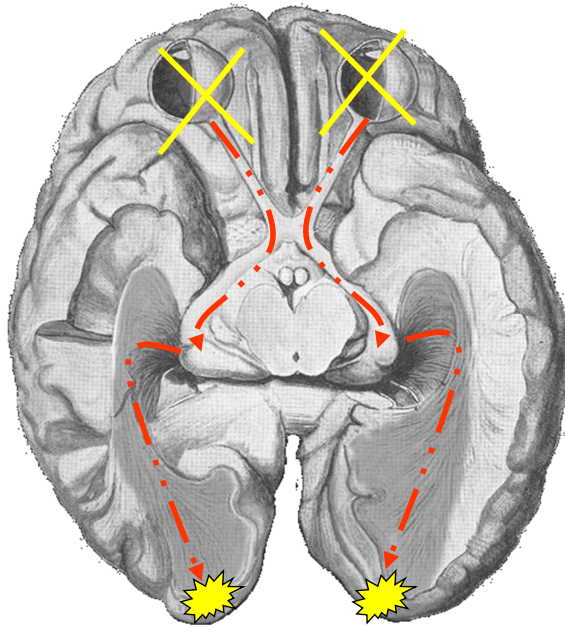


fMRI signal

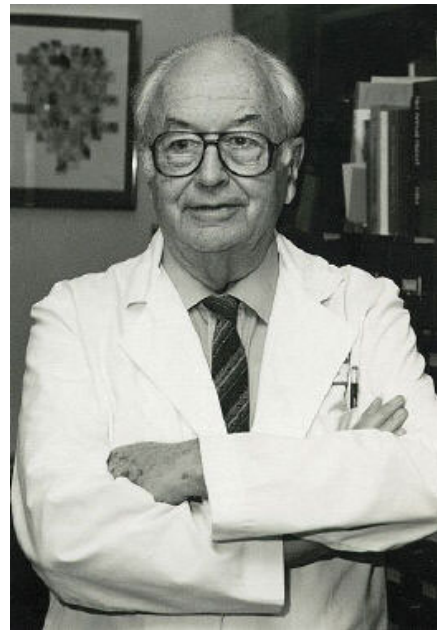


ffytche et al *Nature Neurosci* 1998

## Release / de-afferentation theory

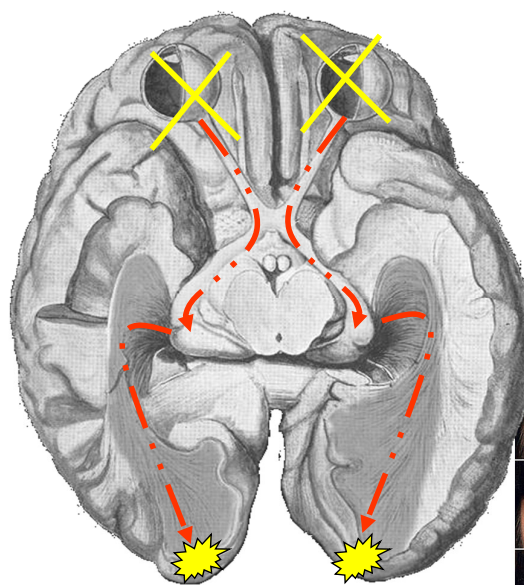


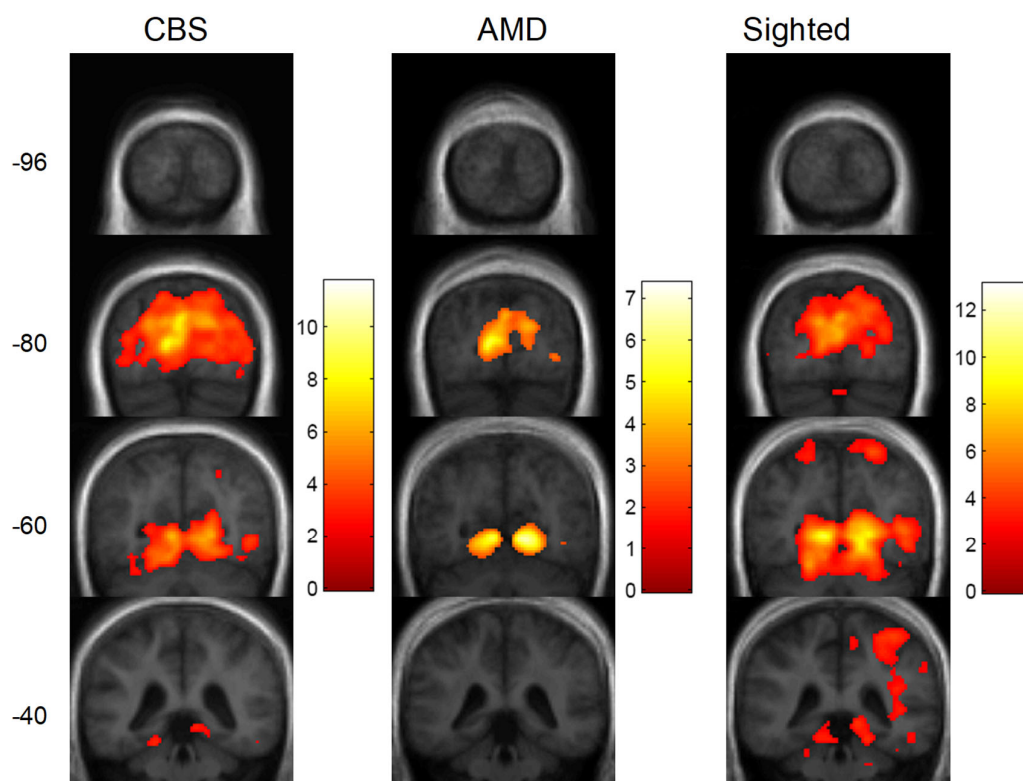
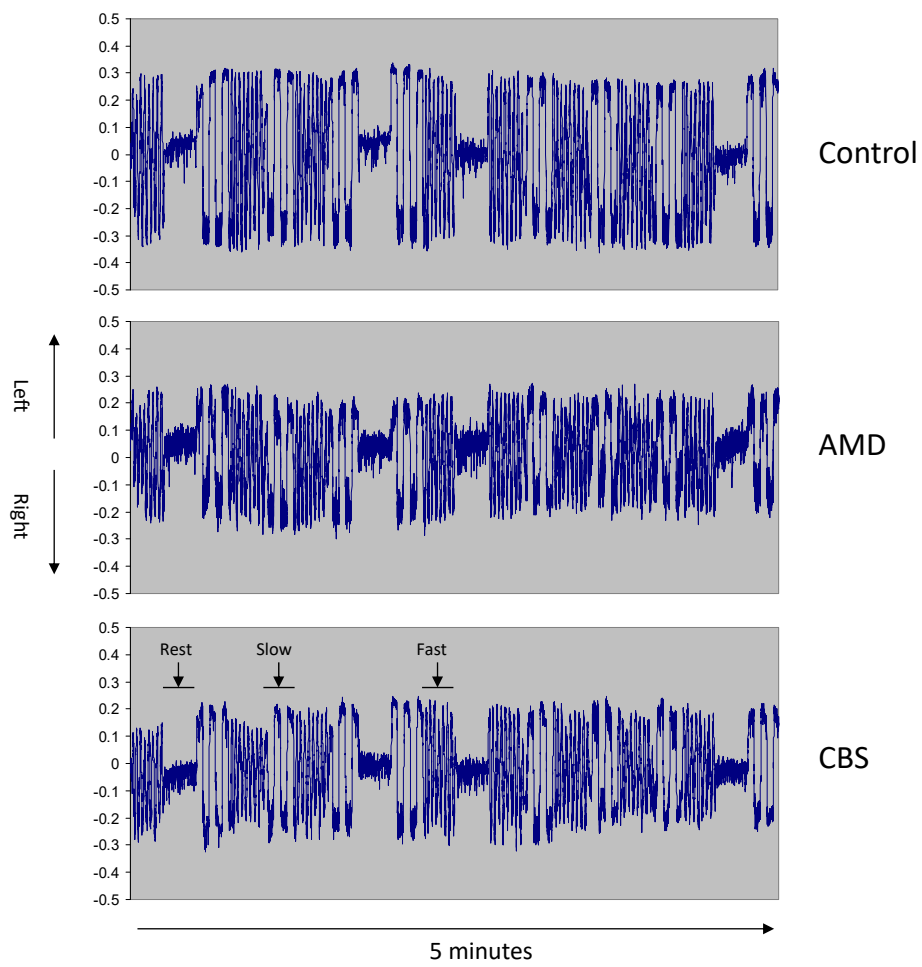
Spontaneous activation  
Hyper-sensitivity



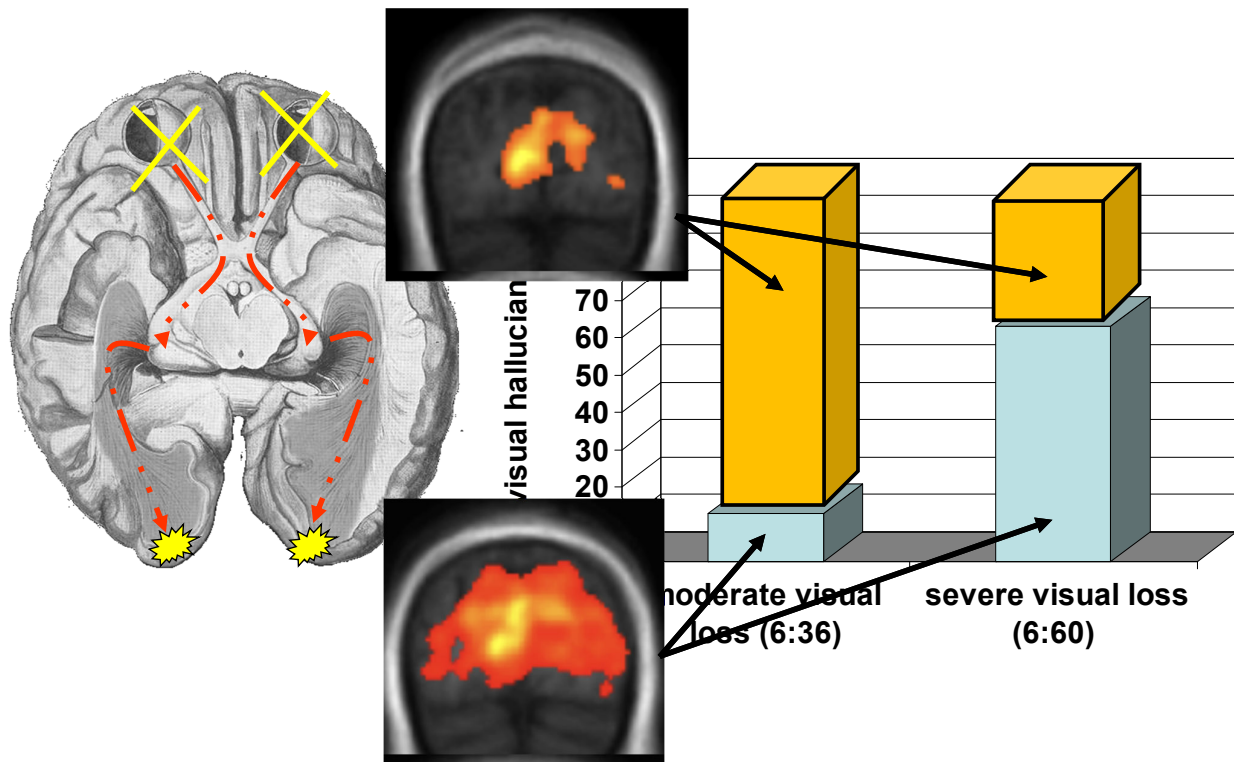
David Cogan  
1908-1993

*Cogan Graefe's Archive, 1973*

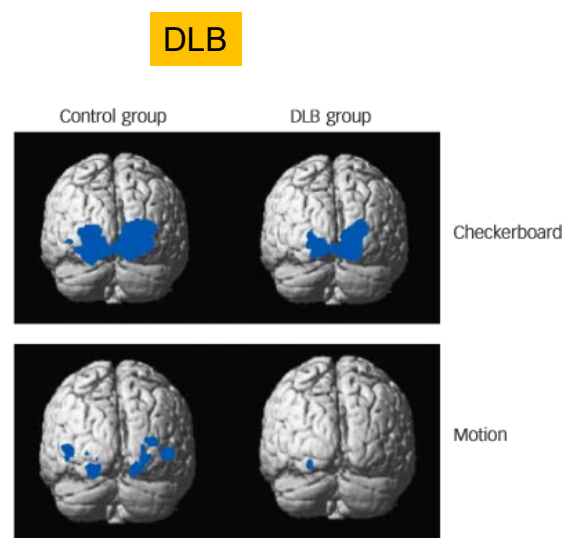
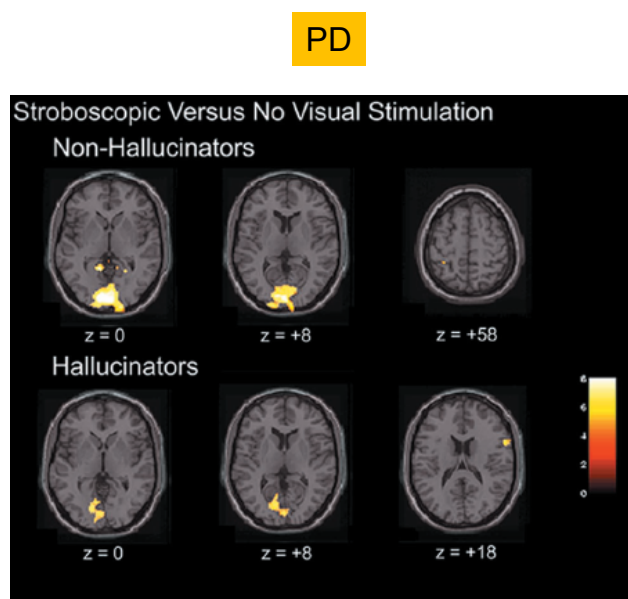


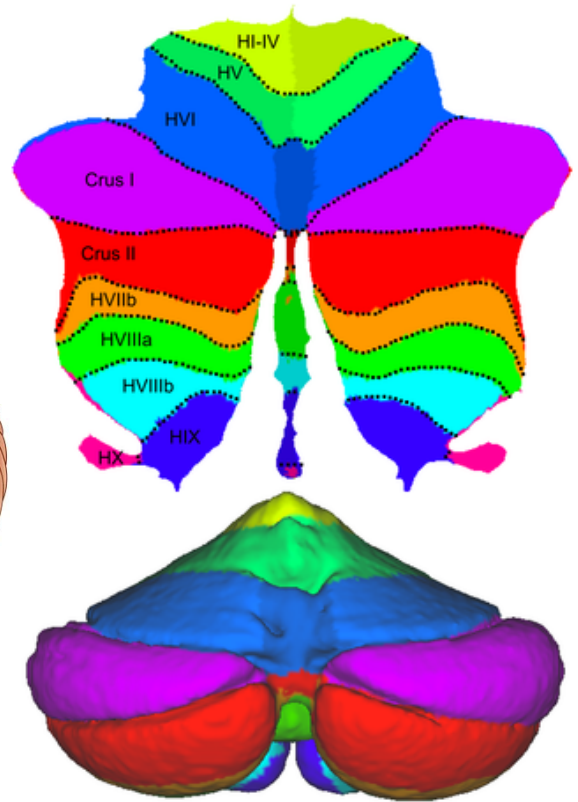


## Release / de-afferentation theory



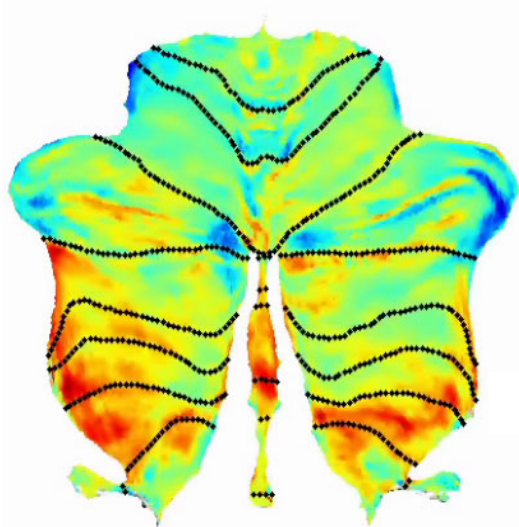
## Decreased occipital excitability – PD DLB



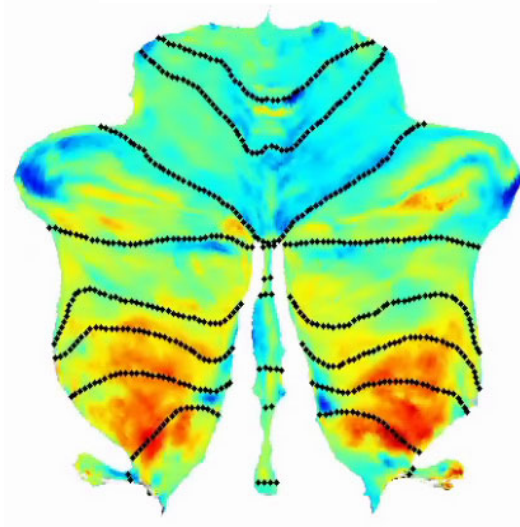


Lawn and ffytche Cortex 2020

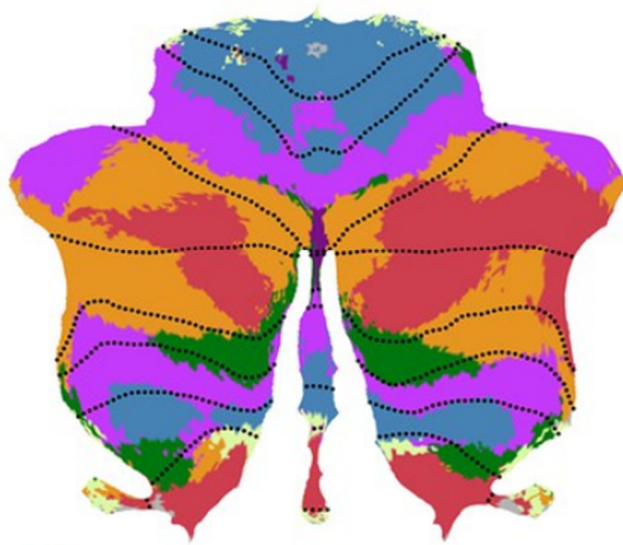
CBS versus AMD



PD-VH versus PD-noVH

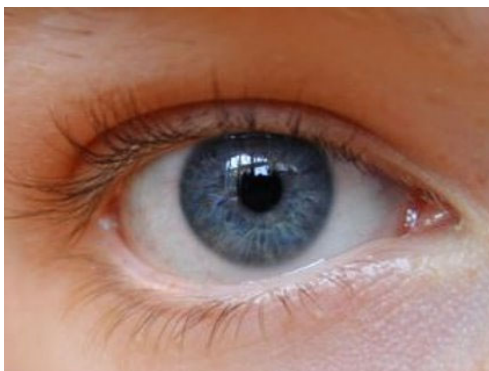


Lawn and ffytche Cortex 2020



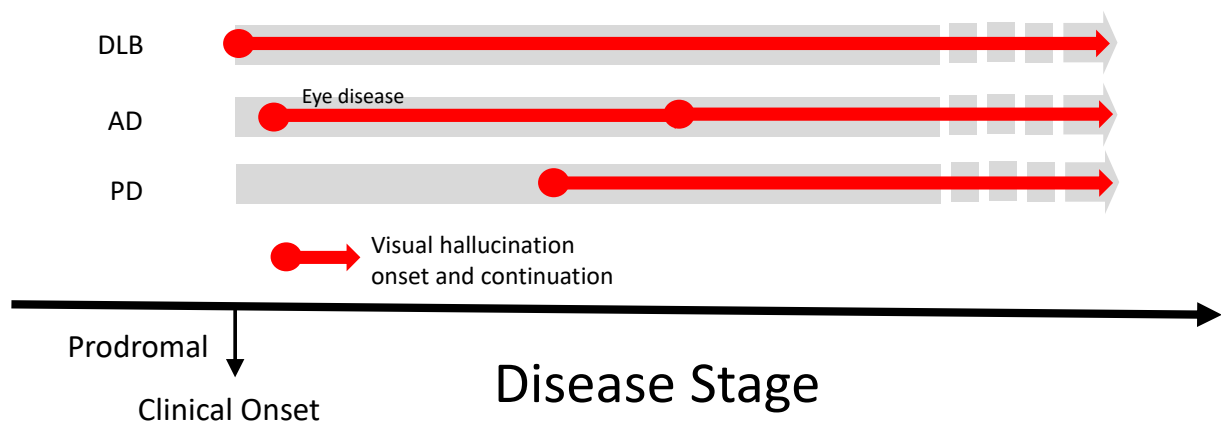
- Somatomotor network
- Ventral Attention network
- Dorsal Attention network
- Limbic network
- Frontoparietal network
- Default Mode network
- Visual network

Guell et al eLIFE 2018



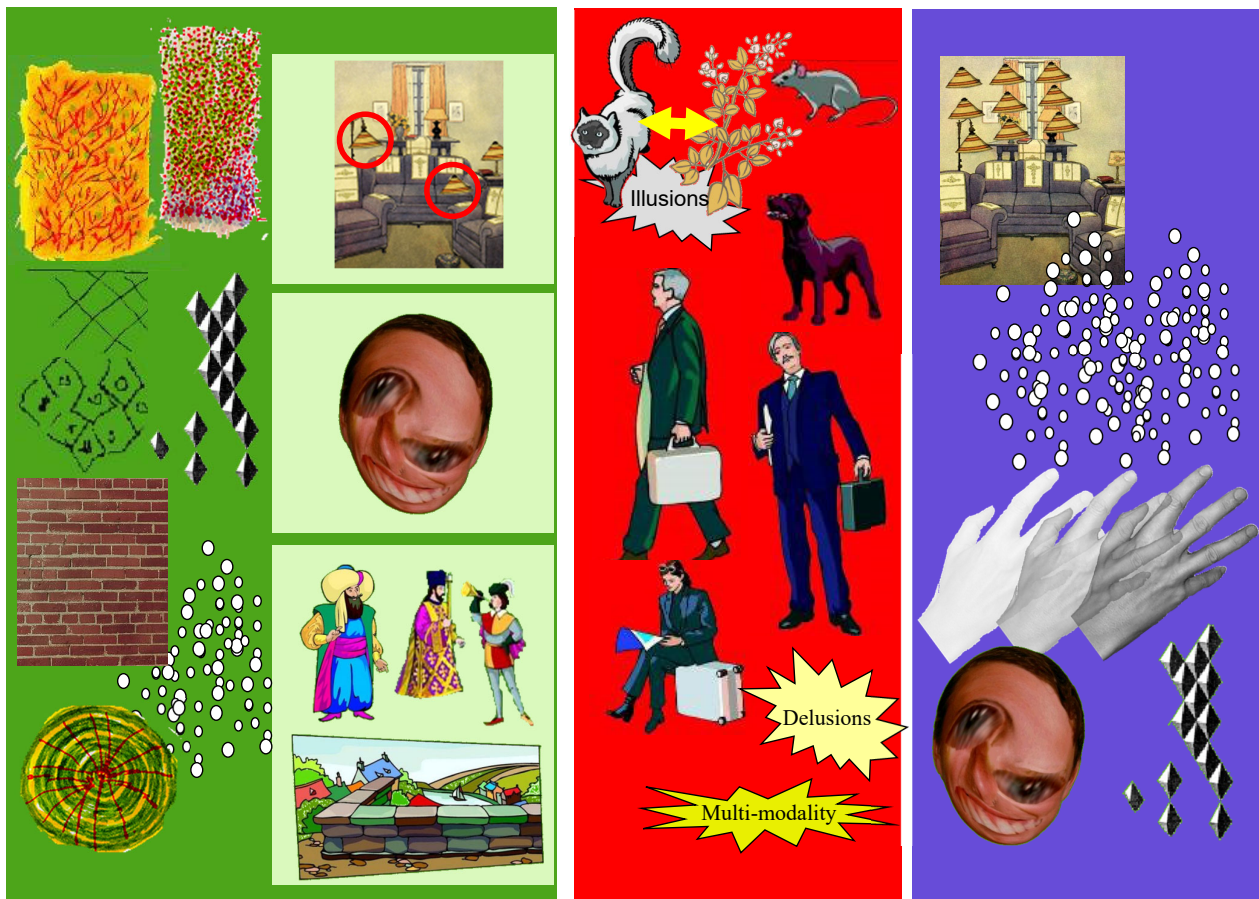
+

Neurodegenerative  
disease



Correlation between clinical and pathological diagnosis

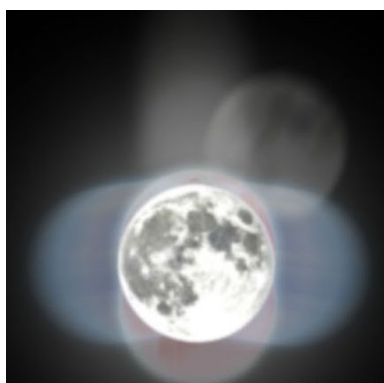
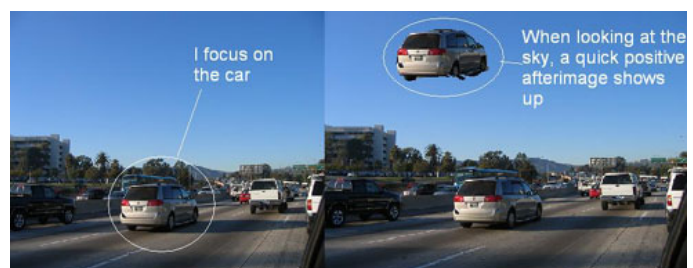
|                        |         | Clinical diagnosis |         |              |          |          |          |          |                | Total |
|------------------------|---------|--------------------|---------|--------------|----------|----------|----------|----------|----------------|-------|
|                        |         | Prob AD            | Poss AD | Mixed AD/VaD | Prob DLB | Poss DLB | Prob PDD | Prob VaD | Other          |       |
| Pathological diagnosis | AD      | 23                 | 0       | 2            | 3        | 1        | 0        | 1        | 1 <sup>#</sup> | 31    |
|                        | DLB/PDD | 2                  | 2       | 0            | 11       | 0        | 5        | 0        | 0              | 20    |
|                        | VaD     | 0                  | 0       | 0            | 0        | 0        | 0        | 2        | 0              | 2     |
|                        | Other   | 1 <sup>\$</sup>    | 0       | 0            | 0        | 0        | 0        | 0        | 2 <sup>+</sup> | 3     |
|                        | Total   | 26                 | 2       | 2            | 14       | 1        | 5        | 3        | 3              | 56    |



ffytche *Dialogues Clin Neurosci* 2007

## Hallucinogen Persisting Perception Disorder

- Palinopsia
- Visual snow
- Halos / ghosting



# Hallucinogen Persisting Perception Disorder

- Palinopsia
  - Visual snow
  - Halos / ghosting
  - Tinnitus
  - Depersonalisation
- 
- Hx Recreational drug use
  - F/H Migraine
  - F/H Psychosis

doi:10.1093/brain/awu050

Brain 2014; 137; 1419–1428 | 1419

**BRAIN**  
A JOURNAL OF NEUROLOGY

## ‘Visual snow’ – a disorder distinct from persistent migraine aura

Christoph J. Schankin,<sup>1,2,\*</sup> Farooq H. Maniyar,<sup>1,2</sup> Kathleen B. Digre<sup>3</sup> and Peter J. Goadsby<sup>1,2</sup>

1 Headache Group, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

2 NIHR-Wellcome Trust Clinical Research Facility, King's College London, London, UK

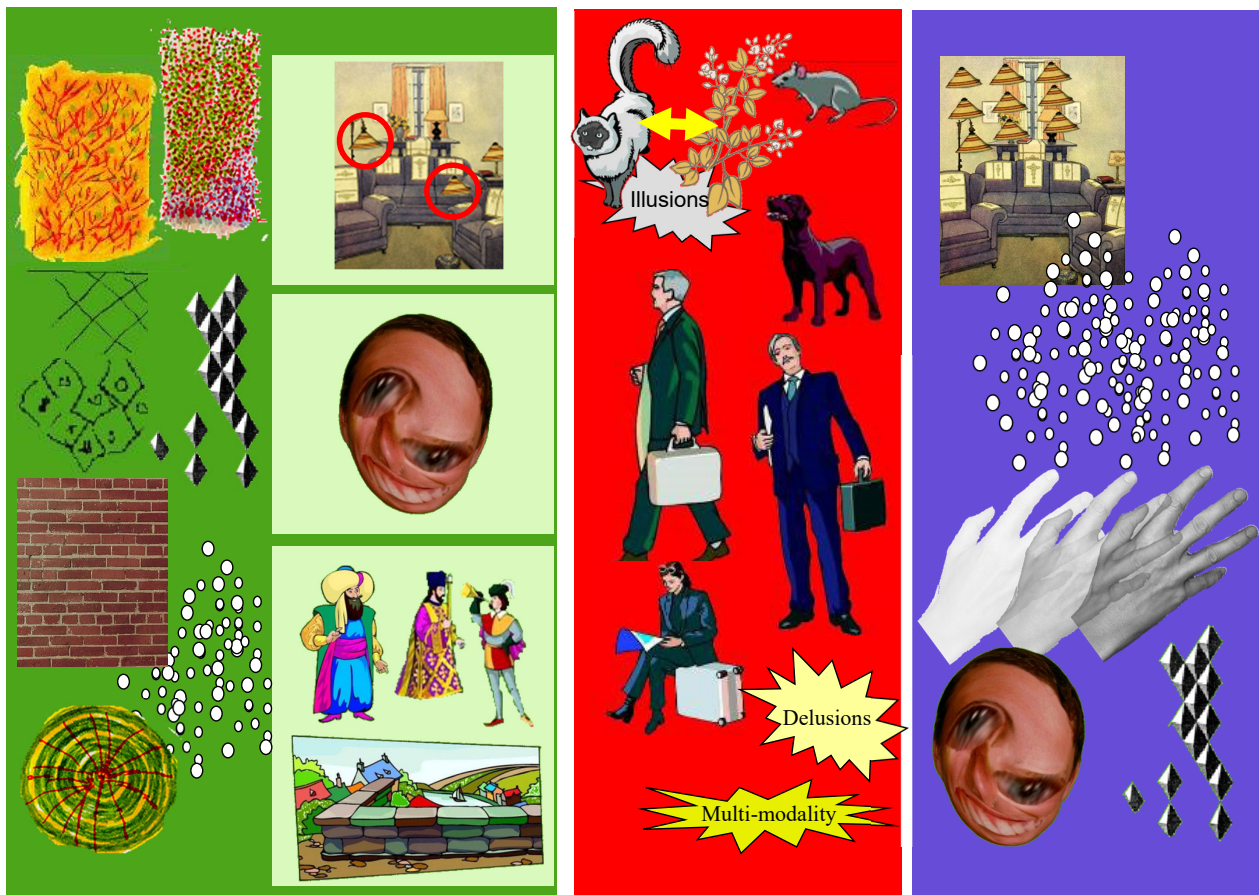
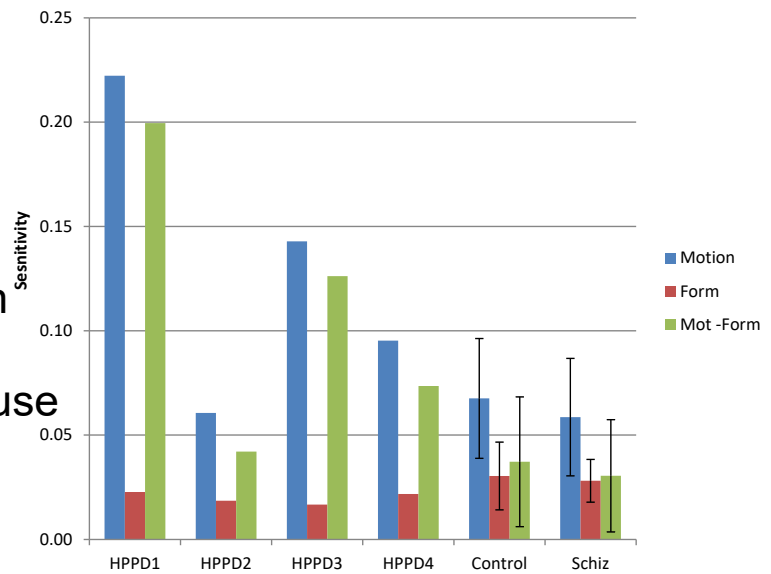
3 Departments of Neurology, Ophthalmology, Moran Eye Centre, University of Utah, Salt Lake City, UT, USA

\*Present address: Department of Neurology, University of Munich Hospital - Großhadern, Munich, Germany

Correspondence to: Prof. Peter J. Goadsby,  
NIHR-Wellcome Trust Clinical Research Facility,  
King's College Hospital,  
London SE5 9PJ, UK  
E-mail: peter.goadsby@kcl.ac.uk

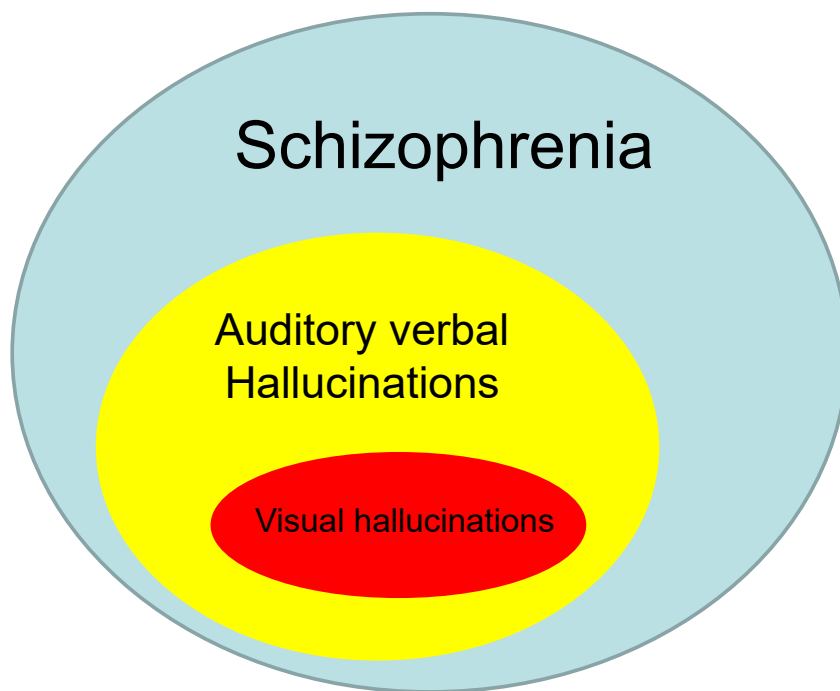
# Hallucinogen Persisting Perception Disorder

- Palinopsia
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  - F/H Psychosis

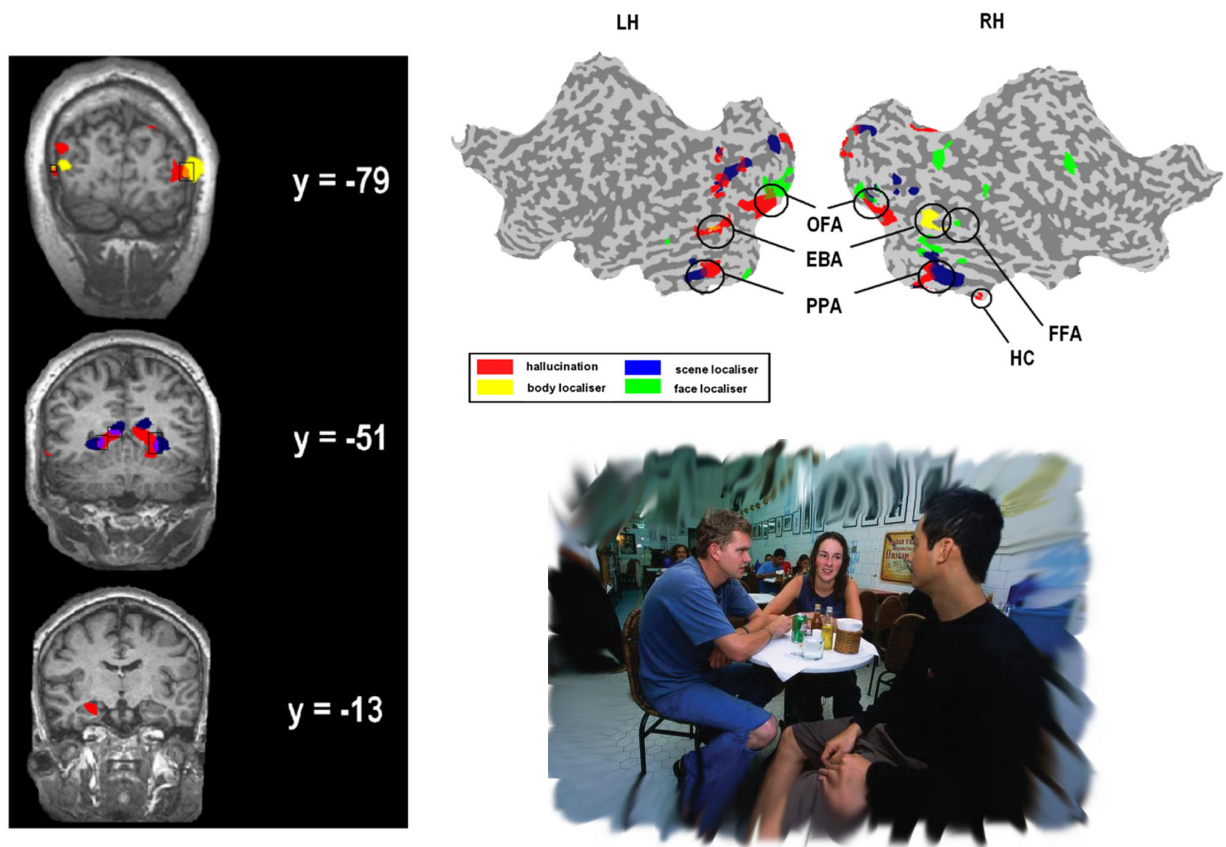


| Symptom | Phenomenology                                                                                                   |
|---------|-----------------------------------------------------------------------------------------------------------------|
| Voices  | 'She thinks rude things', 'She is taking a bath', 'I am going to break your neck' ' Do yourself in'             |
| Visions | people, faces, animals, objects, or events (e.g. fire). Often frightening (bugs, dogs, snakes, distorted faces) |

| Authors                             | n            | Modality of hallucinations |                          |
|-------------------------------------|--------------|----------------------------|--------------------------|
|                                     |              | Visual                     | Auditory                 |
| Bowman & Raymond (1931)             | 1408         | 22%                        | 53%                      |
| Arnold (1949)                       | *            | 14%                        | 78%                      |
| Feinberg (1962)                     | 19           | 4%                         | 84%                      |
| Mallitz, Wilkens, Esecover (1962)   | 100          | 9%                         | 50%                      |
| Vitols, Waters, Keeler (1963)       | 110          | 13%                        | 35%                      |
| Goldberg, Klerman, Cole (1965)      | 270          | 18%                        | 45%                      |
| Mott, Iver, Anderson (1965)         | 50           | 24%                        | 66%                      |
| Small, Small, Anderson (1966)       | 50           | 30%                        | 66%                      |
| Chapman (1966)                      | *            | 40%                        | *                        |
| Holmboe & Astrup (1967)             | 255          | 25%                        | 79%                      |
| Jansson (1968)                      | 293          | 13%                        | 25%                      |
| Goodwin, Alderson, Rosenthal (1971) | 45           | 59%                        | 82%                      |
| Eggers (1973)                       | *            | 44%                        | 71%                      |
| McCabe (1976)                       | 40           | 20%                        | 36%                      |
| Young (1974)                        | 20           | 45%                        | *                        |
| Zarroug (1975)                      | 69           | 47%                        | 62%                      |
| Ciampi & Müller (1976)              | *            | 18%                        | 58%                      |
| McCabe (1976)                       | 25           | 20%                        | 52%                      |
| Deiker, Chambers (1978)             | 28           | 64%                        | 86%                      |
| Huber (1979)                        | *            | 33%                        | 75%                      |
| Ndetei, Singh (1983)                | 51           | 43%                        | 43%                      |
| Ndetei (1984)                       | 141          | 15%                        | 41%                      |
| Winokur et al. (1985)               | 140          | 32%                        | 78%                      |
| Phillipson & Harris (1985)          | 73           | 62%                        | 44%                      |
| Bracha, Wolkowitz et al. (1989)     | 43           | 56%                        | 42%                      |
| Owens & Slade (1989)                | *            | 29%                        | 63%                      |
| Mueser et al. (1990)                | 117          | 14%                        | 71%                      |
| Jablensky et al. (1992)             | 1288         | 30%                        | 55%                      |
| Bauer et al. (2011)                 | 1238         | 34%                        | 79%                      |
| <b>Total: 29 studies</b>            | <b>5,873</b> | <b>Weighted Mean 27%</b>   | <b>Weighted Mean 59%</b> |

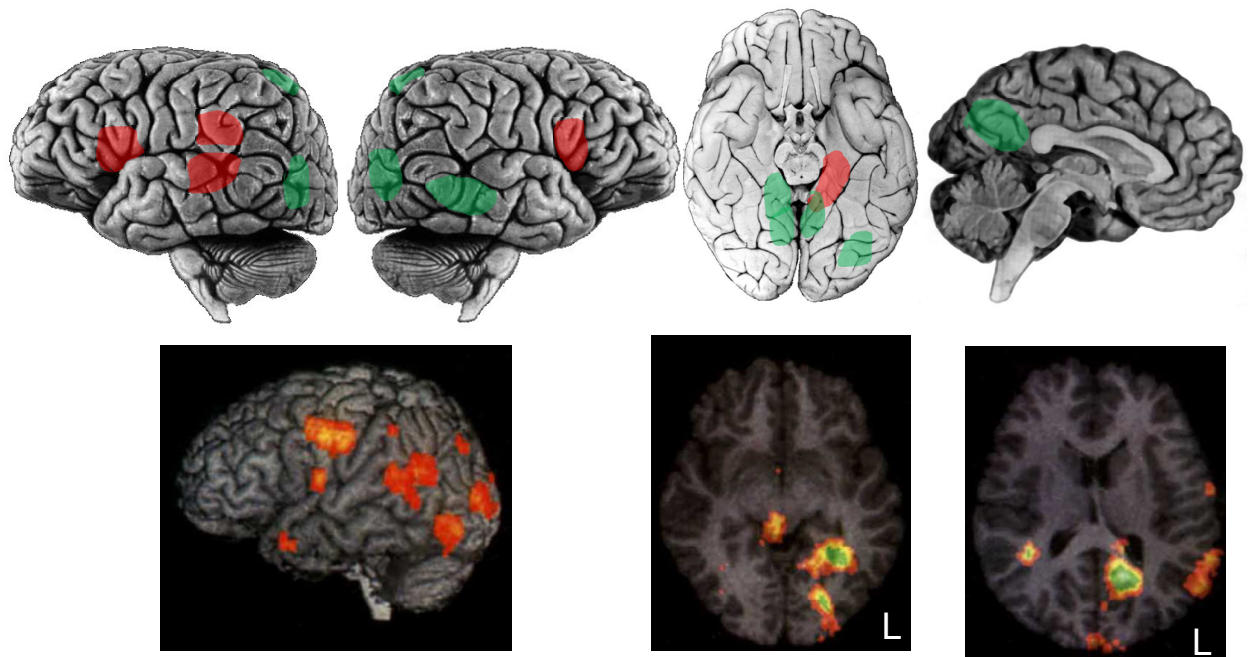


| Symptom                 | Phenomenology                                                                                                   |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|
| Voices                  | 'She thinks rude things', 'She is taking a bath', 'I am going to break your neck' ' Do yourself in'             |
| Visions                 | people, faces, animals, objects, or events (e.g. fire). Often frightening (bugs, dogs, snakes, distorted faces) |
| Multimodal              |                                                                                                                 |
| Sequential Unimodal     | 50% of schizophrenia                                                                                            |
| Perceptually un-related | man running towards me with a knife and an ethereal voice from elsewhere telling me I am about to be killed     |
| Perceptually related    | Disembodied heads speaking and giving instructions                                                              |
|                         |                                                                                                                 |



Oertel et al *Psych Res Neuroimaging* 2007

## Multimodal hallucinations





SHAPED

Study of **H**Allucinations in **P**arkinson's disease, **E**ye disease and **D**ementia



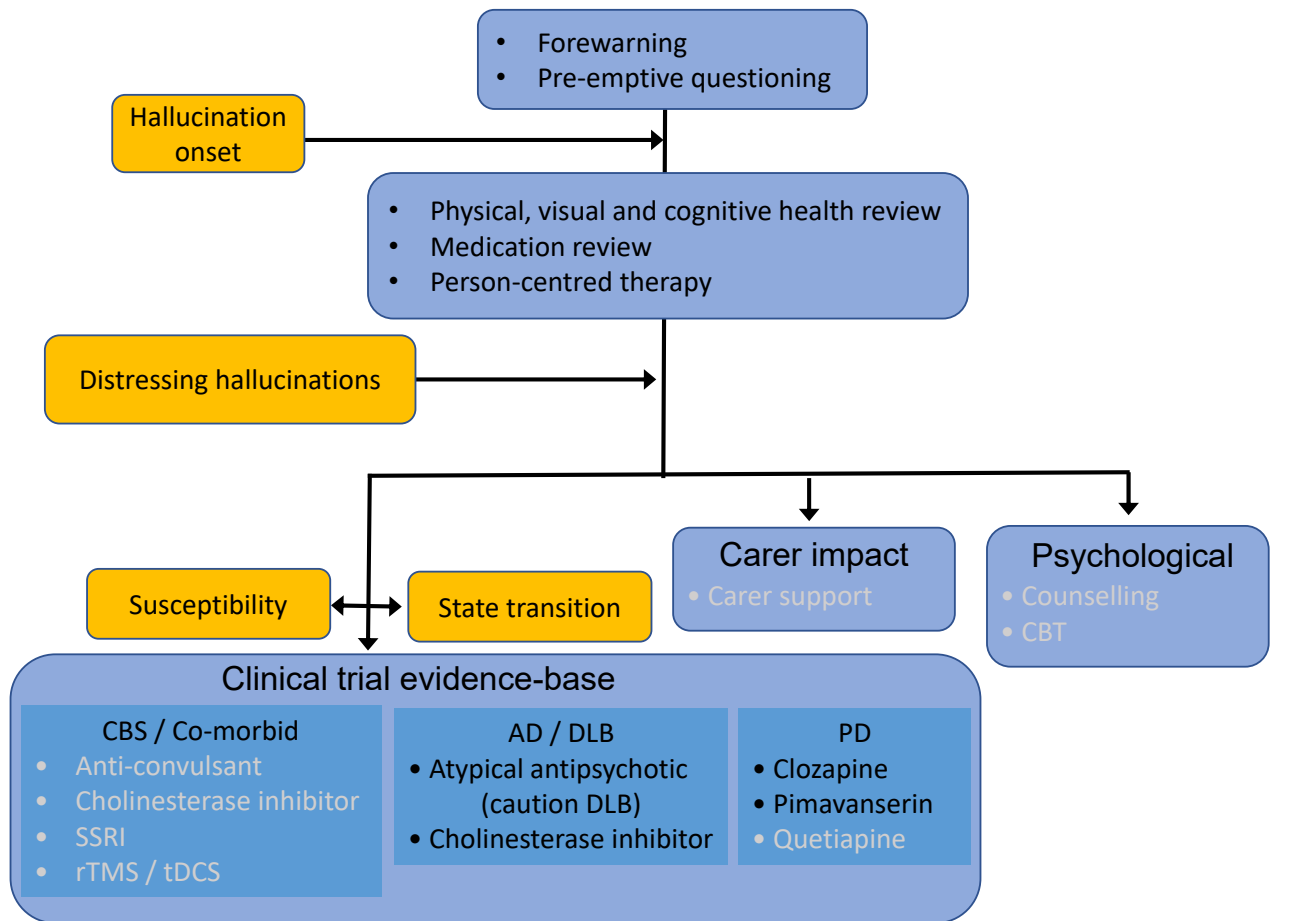
Neurodegeneration



REVIEW

## Visual hallucinations in neurological and ophthalmological disease: pathophysiology and management

John O'Brien <sup>1</sup>, John Paul Taylor <sup>2</sup>, Clive Ballard,<sup>3</sup> Roger A Barker,<sup>4</sup> Clare Bradley,<sup>5,6</sup> Alistair Burns,<sup>7</sup> Daniel Collerton,<sup>2</sup> Sonali Dave,<sup>8</sup> Rob Dudley,<sup>9</sup> Paul Francis,<sup>3,8</sup> Andrea Gibbons,<sup>6</sup> Kate Harris <sup>4</sup>, Vanessa Lawrence,<sup>8</sup> Iracema Leroi,<sup>10</sup> Ian McKeith,<sup>2</sup> Michel Michaelides,<sup>11,12</sup> Chaitali Naik,<sup>11</sup> Claire O'Callaghan,<sup>13</sup> Kirsty Olsen,<sup>2</sup> Marco Onofrij,<sup>14</sup> Rebecca Pinto,<sup>8</sup> Gregor Russell,<sup>15</sup> Peter Swann,<sup>1</sup> Alan Thomas,<sup>2</sup> Prabitha Urwyler,<sup>16,17</sup> Rimona Sharon Weil <sup>18</sup>, Dominic ffytche <sup>8</sup>



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- Physical, visual and cognitive health review
- Medication review
- Person-centred therapy

## Physical health review

- Delirium screen

## Cognitive review

- MCI / dementia screen

## Optimising vision

- Optimal refraction
- Low vision aids
- Ophthalmological intervention

- Physical, visual and cognitive health review
- **Medication review**
- Person-centred therapy

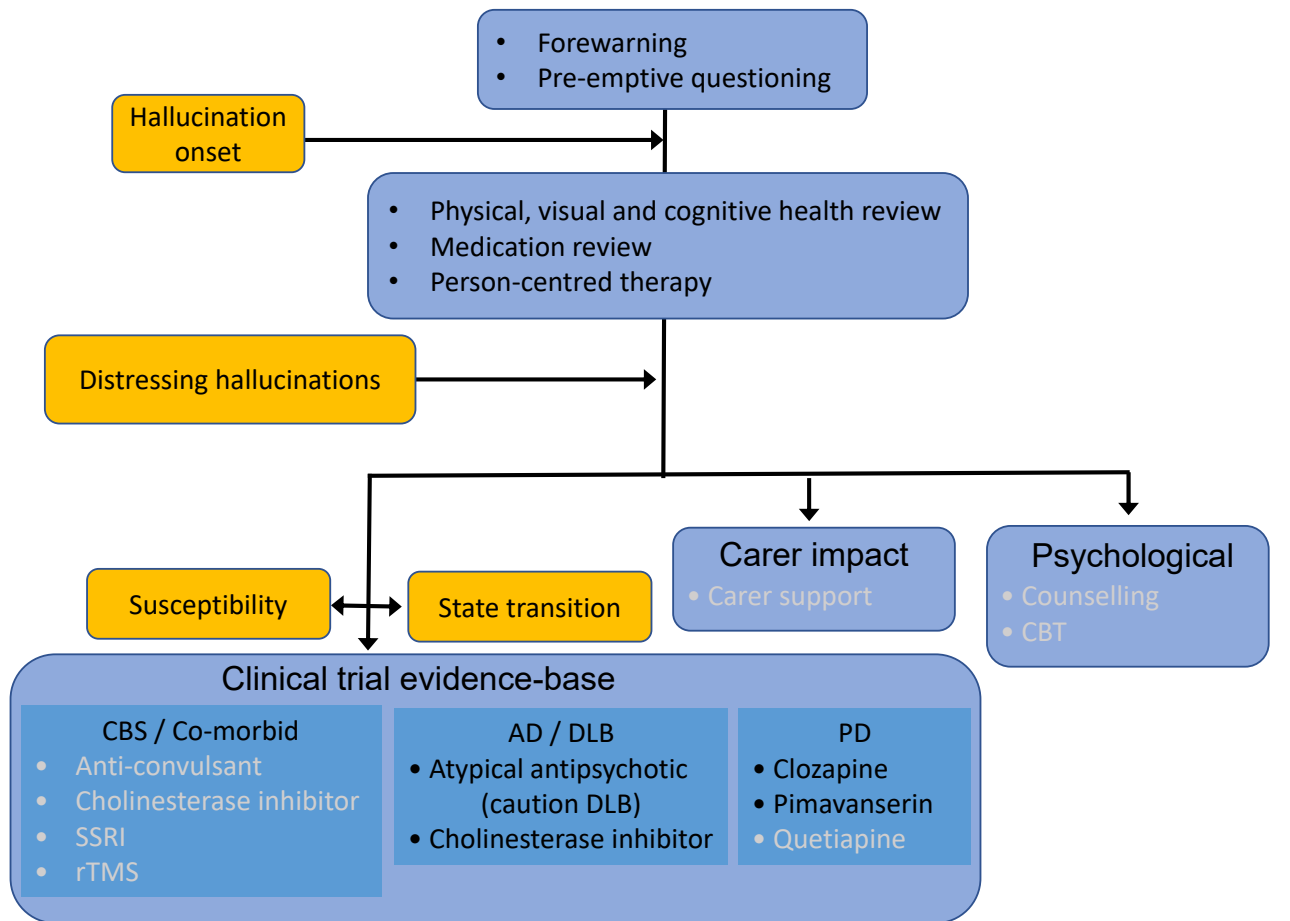
## Medication review

- Anticholinergic medication
- PD medication
- Opiates

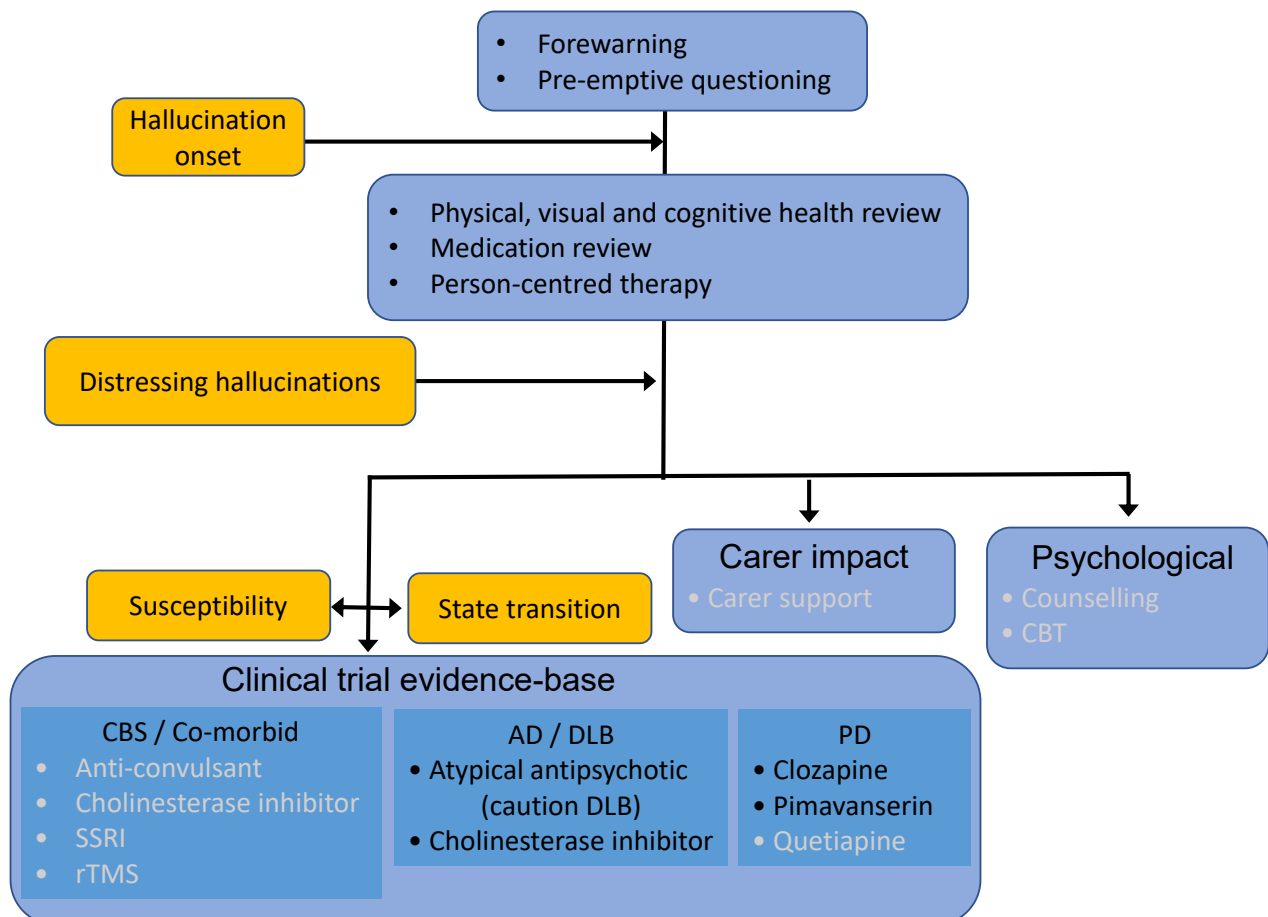
- Physical, visual and cognitive health review
- Medication review
- **Person-centred therapy**

## Stopping a hallucination

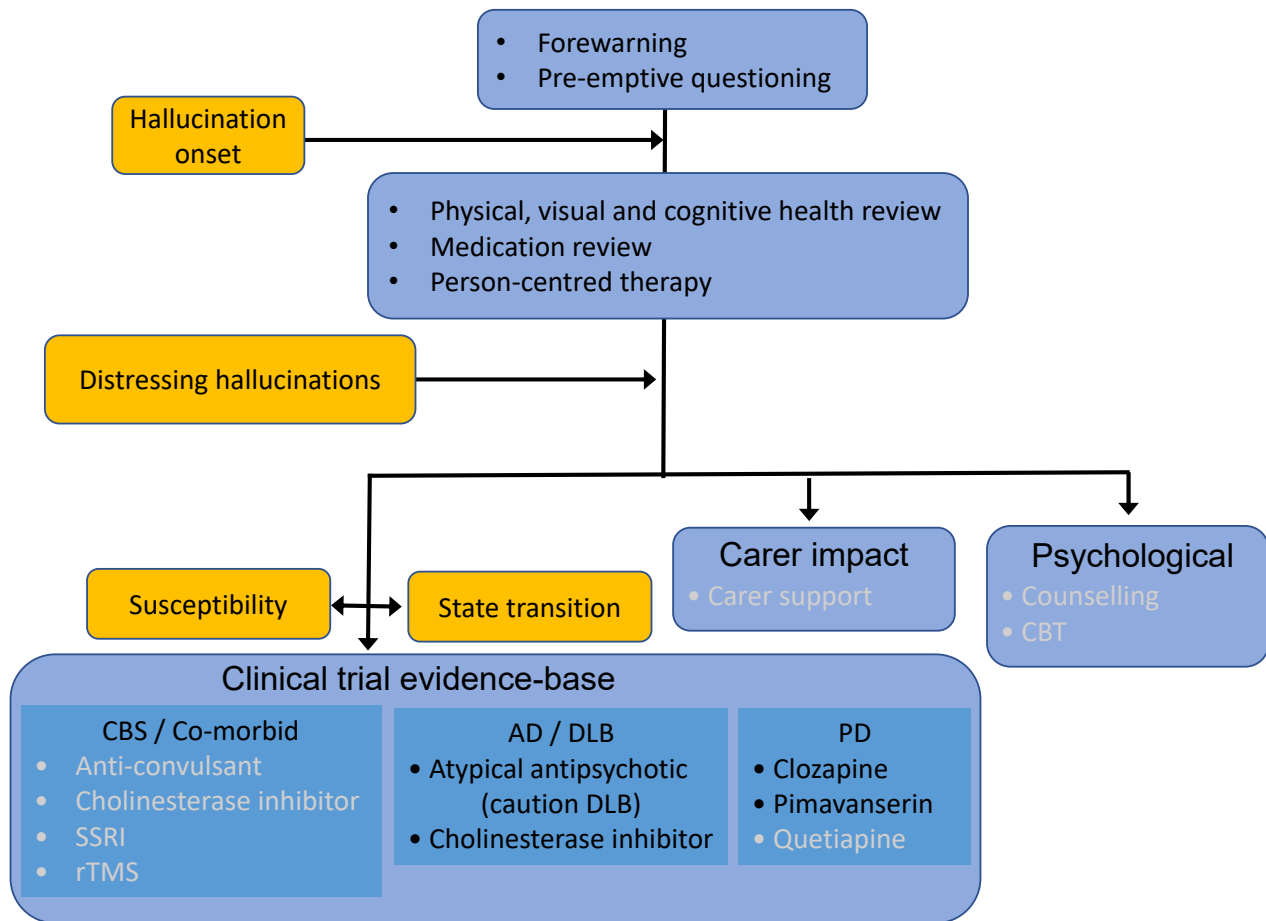
- Alerting
- Lighting
- Eye movements



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