
بسم الله الرحمن الرحیم

Dementia-Related Psychosis

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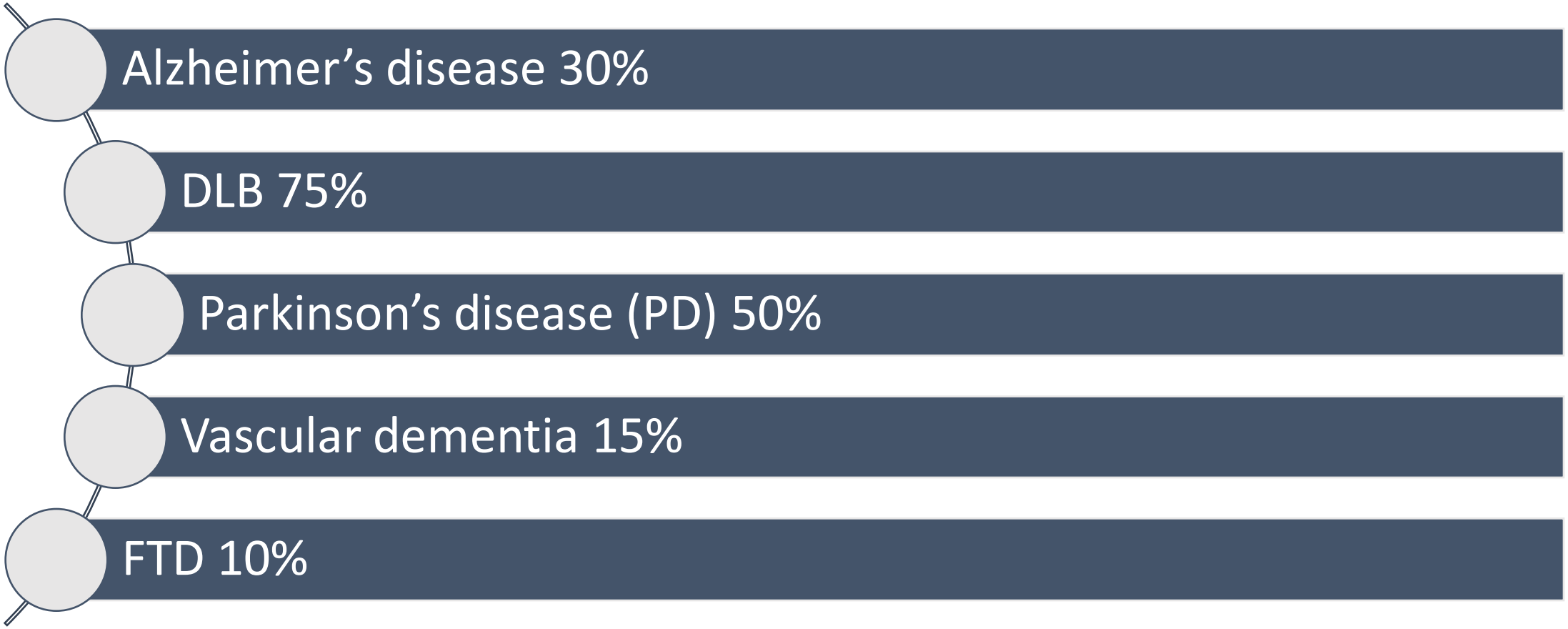
- Late onset psychosis as a prodromal symptom to neurodegeneration,
- Late onset psychosis can also be associated with nonprogressive mild cognitive deficit.
- Studies found associations between late-life psychosis and incident dementia.
- Interestingly, in a prospective population-based cohort of 23,999 men aged 65–85 years, psychosis was associated with a substantial risk of dementia, most notably in individuals with a shorter duration of psychosis.

- Late onset psychosis often associated with Alzheimer’s type Dementia (AD) or Dementia with Lewy Bodies (DLB)
- Irrespective of the etiopathology, psychosis with onset in late life is less frequently accompanied by negative symptoms such as affective flattening or disorganized thought

Sequelae of dementia-related psychosis

- Hospitalization or institutionalization
- Cognitive and functional impairment,
- Accelerated cognitive decline
- Mortality
- Caregiver distress

Prevalence of Psychosis in NCD



Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition. Am J Geriatr Psychiatry.2020

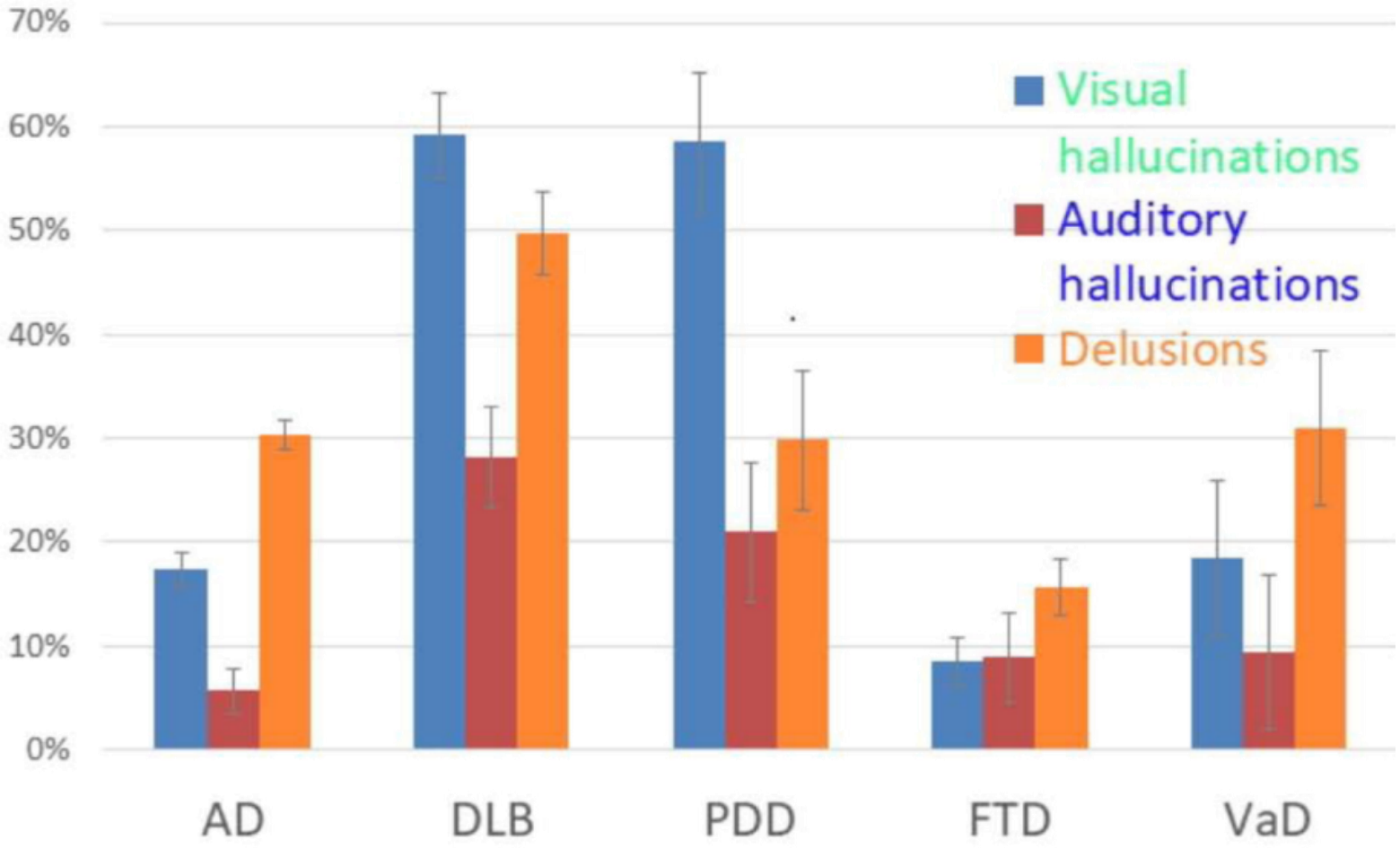


Figure 1.
Prevalence of hallucinations and delusions in major types of dementia (contributed by Dr. Debby Tsuang and Andrew Shutes-David).

Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition. Am J Geriatr Psychiatry.2020

Diagnostic criteria for psychosis of AD, 2000.

A. *Characteristic Symptoms*

Presence of one (or more) of the following symptoms:

1. Visual or auditory hallucinations

2. Delusions

B. *Primary Diagnosis*

All the criteria for dementia of the Alzheimer type are met

C. *Chronology of the onset of symptoms of psychosis vs. onset of symptoms of dementia*

There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia

D. *Duration and Severity*

The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning.

E. *Exclusion of schizophrenia and related psychotic disorders*

Criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Mood Disorder with Psychotic Features have never been met

F. *Relationship to delirium*

The disturbance does not occur exclusively during the course of a delirium

G. *Exclusion of other causes of psychotic symptoms*

The disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (e.g., a drug of abuse, a medication)

Associated features: *(Specify* if associated)

With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression

With Negative Symptoms: when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present

With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present

Limitation of Previous Criteria

- Lack specificity regarding severity and duration of symptoms
- Exclude patients who exhibit psychotic symptoms prior to a dementia diagnosis

Psychosis across the cognitive spectrum

Mild Behavioural Impairment

- MBI is a validated syndrome characterized by late onset of persistent NPS, representing a change from longstanding patterns of behaviour, as an at-risk state for incident cognitive decline and dementia.
- Psychosis seems to be one of the least frequent but carries the highest risk of cognitive decline.

Table 1 ISTAART research diagnostic criteria for Mild Behavioral Impairment

1. Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥ 50 years) and persisting at least intermittently for ≥6 months. These represent a clear change from the person's usual behavior or personality as evidenced by at least one of the following:
a. Decreased motivation (e.g., apathy, aspontaneity, indifference)
b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
e. Abnormal perception or thought content (e.g., delusions, hallucinations)
2. Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
a. Interpersonal relationships
b. Other aspects of social functioning
c. Ability to perform in the workplace
The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
1. Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
2. The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Abbreviations: ISTAART (Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment)

Table 2 | **Frequency of psychosis across the cognitive spectrum**

Cognitive status	Phenomenology	Prevalence
Late-onset psychosis assessed in the mild behavioural impairment framework in people with normal cognition	Only one study conducted; suspicious thoughts were the prevailing symptom; other symptoms were present but at very low frequencies	5% if rated by proxy, 2.5% if self-rated (suspicious thoughts ~2–4%, visual hallucinations, auditory hallucinations, grandiose delusions and persecutory delusions 0.1–0.8%)
Mild cognitive impairment	Persecutory delusions and visual hallucinations are the most common symptoms	Delusions 3.1–10.5%, hallucinations 1.3–2.6%
Dementia	Persecutory delusions of theft, spousal infidelity. and personal harm and misidentification; first-rank symptoms (for example, thought insertion, withdrawal and broadcasting) are very rare; hallucinations are predominantly visual and involve people, animals or objects	41% (23% delusions only, 5% hallucinations only, 13% both)

Revised criteria for psychosis in major or mild neurocognitive disorder.

A. *Characteristic Symptoms*

Presence of one (or more) of the following symptoms:

1. Visual or auditory hallucinations (e.g., seeing silent individuals standing in the room, seeing children in the yard, or seeing animals in the house)

2. Delusions (fixed false beliefs that the patient believes to be true, e.g. that the spouse is unfaithful, that possessions are being stolen, or that one is not who one claims to be)

B. *Primary Diagnosis*

All the criteria for any major and mild neurocognitive disorder are met, with the etiologic diagnoses specified (e.g., major neurocognitive disorder (Alzheimer's disease)). Specific diagnoses include Alzheimer's disease, dementia with Lewy bodies, vascular dementia, Parkinson disease dementia, frontotemporal dementia, progressive supranuclear palsy, mild cognitive impairment, traumatic brain injury, and corticobasal degeneration. Other rarer causes of major and mild neurocognitive disorder are also appropriate when diagnosed as a cause of psychosis.

C. *Chronology of the onset of symptoms of psychosis vs. onset of symptoms of*

cognitive impairment

There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia

D. *Duration*

The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer.

E. Severity

Symptoms are severe enough to cause some disruption in patients' and/or others' functioning or pose a threat to the safety of self or others. "Disruption" is defined as interfering with the

patient's or others' ability to accomplish activities of daily living or interact as usual socially; "patient's functioning" is defined as being able to interact with family members and others, not being preoccupied with hallucinations, etc.; "other's functioning" is defined as interfering with the ability of others to care for or interact with the patient or causing distress to the partner.

F. **Exclusionary Criteria**

1. Patients who have met the criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, Mood Disorder with PF, or Depression with PF.

2. When the psychosis occurs exclusively during the course of a delirium.

3. When the psychosis is solely attributable to another general-medical condition (e.g., hypothyroidism) or direct physiological effects of a substance (e.g., a drug of abuse, a medication).

4. When the symptoms are culturally appropriate (e.g., ancestor hallucinations in some cultures).

5. When the hallucinations are more readily attributable to conditions known to cause hallucinations such as epilepsy, migraine, disease of the sensory organs, or stroke.

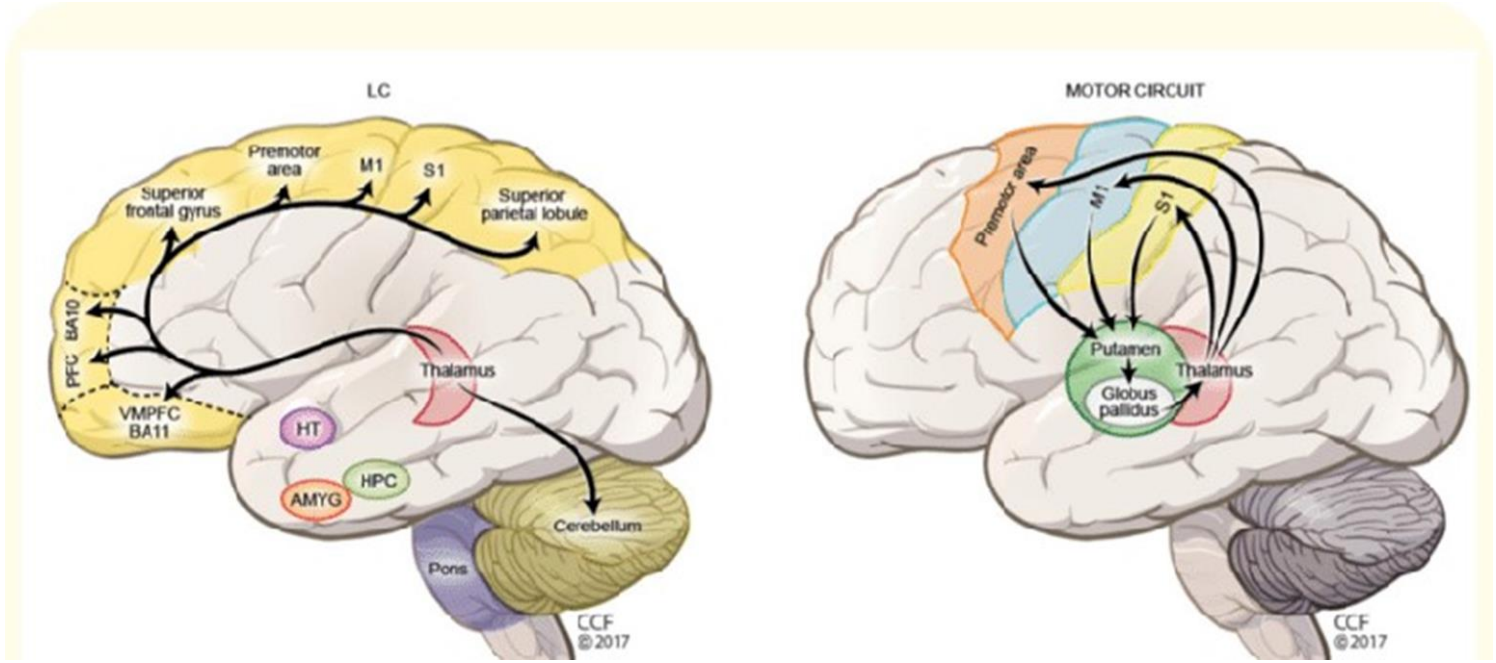
G. **Associated features**: (Specify if associated)

With Agitation

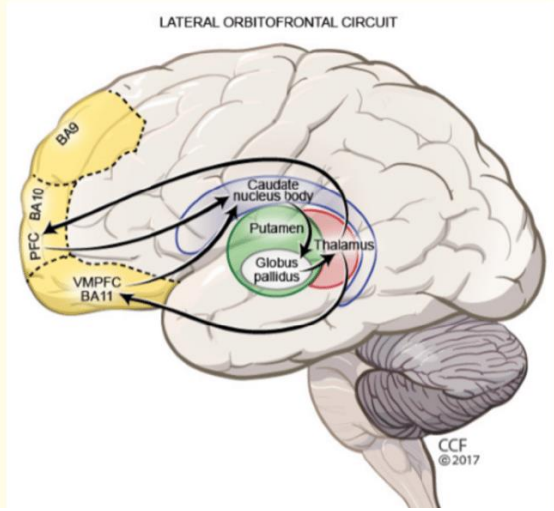
With Depression

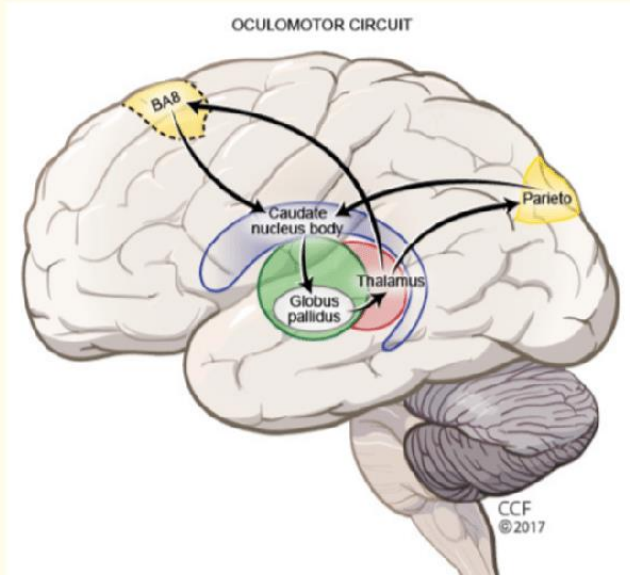
Neurobiological and (Neuro)Psychological Underpinnings of Late Onset Psychosis

- Onset of both delusions and hallucinations in late life reflects disturbances in the frontal-subcortical temporal brain systems transdiagnostically in Schizophrenia-like illnesses and neurodegenerative conditions
- In addition,frontotemporal abnormalities in the most frequently occurring neurodegenerative conditions in late life such as AD or DLB with psychotic symptoms also supersede those observed in AD or DLB without such symptoms.


LC
Premotor area
M1
S1
Superior frontal gyrus
Superior parietal lobule
PFC BA10
VMPFC BA11
Thalamus
HT
HPC
AMYG
Cerebellum
Pons
CCF ©2017

MOTOR CIRCUIT
Premotor area
M1
S1
Putamen
Thalamus
Globus pallidus
CCF ©2017


LATERAL ORBITOFRONTAL CIRCUIT
BA9
BA10
PFC
Caudate nucleus body
Putamen
Thalamus
Globus pallidus
VMPFC BA11
CCF ©2017


OCULOMOTOR CIRCUIT
BA8
Caudate nucleus body
Parieto
Thalamus
Globus pallidus
CCF ©2017

Features that may distinguish neurodegenerative causes of psychosis from non-neurodegenerative causes

- Variable persistence of symptoms
- Visual hallucinations
- Misidentification

Unified Transdiagnostic Approach to NCD- related psychosis

- Phenotypic definition
- Use of antipsychotics across dementia diagnose
- Diagnostic overlap
- Shared biology:
- Autopsy series show that among patients with a diagnosis of AD in life:
  - 30% have AD as the only pathology at the time of autopsy.
  - 70% have mixtures of vascular lesions, TAR DNA-binding protein-43 (TDP-43), and alpha-synuclein with the pathological changes of AD.
- This overlap of pathologies may contribute to shared pathogenesis of clinical syndromes among NCDs including psychosis.

- Even though a slightly differing presentation of psychotic symptoms may already prove useful in differential diagnosis, an overlap in the phenomenology of psychosis in different diseases is still important, creating the need for further investigation.

- The presence of psychosis, combined with clinicians' preconceived notions about psychosis and dementia, can influence a dementia diagnosis.
- In a study of 961 neuropathologically confirmed cases of AD in the NACC database, the presence of psychosis in individuals with AD was associated with a fivefold increased likelihood of misdiagnosis of the condition as DLB, suggesting that clinicians tend to favour a DLB diagnosis in the presence of psychosis.

CNS Spectrums

www.cambridge.org/cns

Perspectives

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Dementia-related psychosis and the potential role for pimavanserin

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Abstract

Dementia-related psychosis (DRP) is prevalent across dementias and typically manifests as delusions and/or hallucinations. The mechanisms underlying psychosis in dementia are unknown; however, neurobiological and pharmacological evidence has implicated multiple signaling pathways and brain regions. Despite differences in dementia pathology, the neurobiology underlying psychosis appears to involve dysregulation of a cortical and limbic pathway involving serotonergic, gamma-aminobutyric acid ergic, glutamatergic, and dopaminergic signaling. Thus, an imbalance in cortical and mesolimbic excitatory tone may drive symptoms of psychosis. Delusions and hallucinations may result from (1) hyperactivation of pyramidal neurons within the visual cortex, causing visual hallucinations and (2) hyperactivation of the mesolimbic pathway, causing both delusions and hallucinations. Modulation of the 5-HT_{2A} receptor may mitigate hyperactivity at both psychosis-associated pathways. Pimavanserin, an atypical antipsychotic, is a selective serotonin inverse agonist/antagonist at 5-HT_{2A} receptors. Pimavanserin may prove beneficial in treating the hallucinations and delusions of DRP without worsening cognitive or motor function.

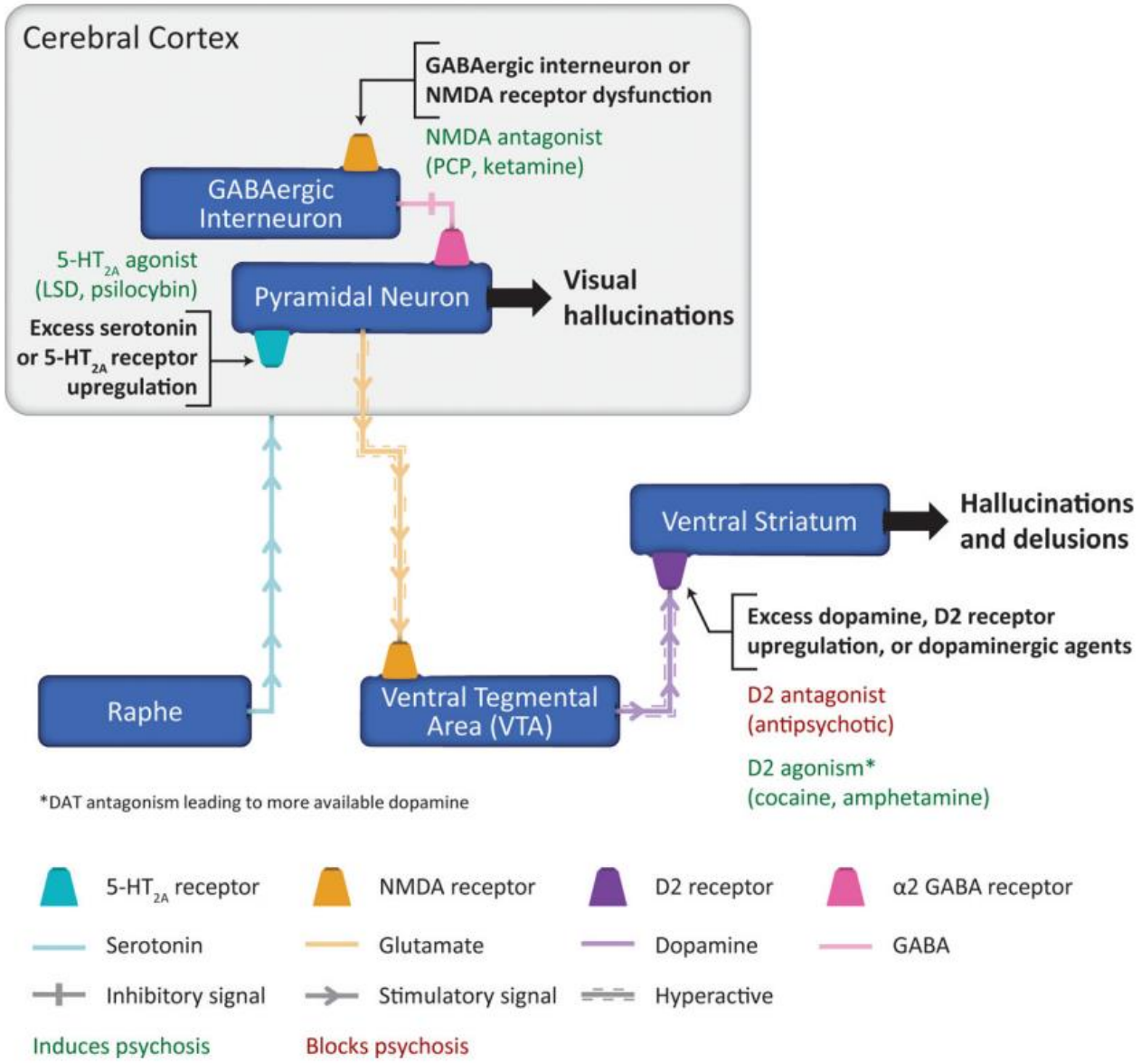


Figure 1. Hypothesized cortical–limbic psychosis pathway and proposed mechanism of disease for DRP. Dementia-related psychosis and the potential role for pimavanserin.

- Schizophrenia-like illnesses in late life compared to normally aging individuals are associated with:
- Increased ventricle-to-brain ratio
- White matter pathology
- Functional and structural abnormalities in the frontal-subcortical temporal region

Factors that Trigger Psychosis in NCD

Medical conditions

- Pain
- Physical discomfort
- UTI
- Constipation
- Delirium
- polypharmacy

Environmental Factors

- overstimulation
- Social Isolation

Personal Factors

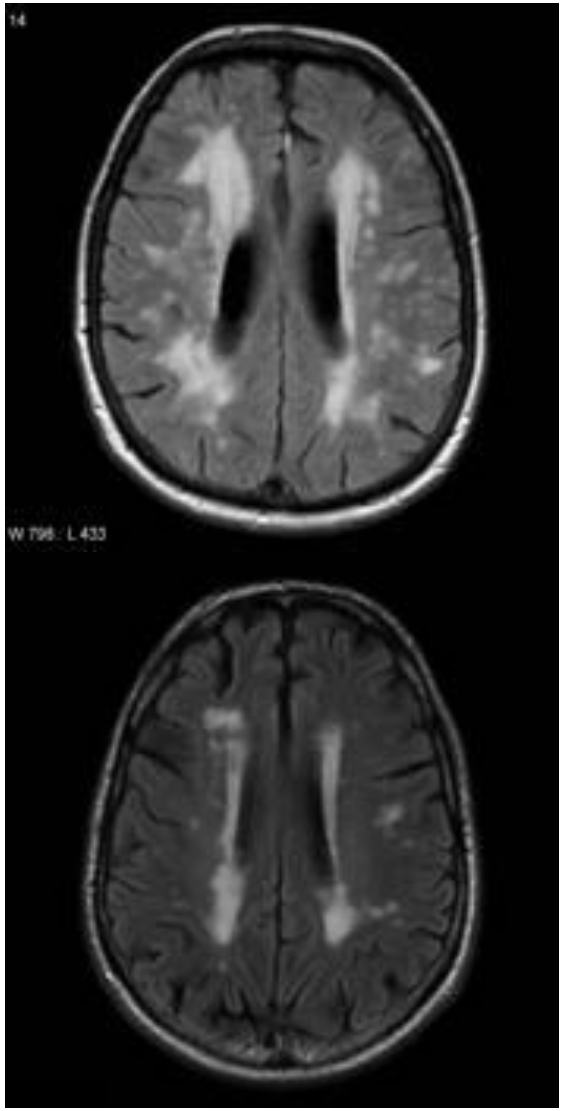
- Premorbid Personality
- Maladaptive coping mechanisms

Behavioural and Psychological symptoms of Dementia (BPSD)

- Neuropsychiatric symptoms (NPS) are almost ubiquitous in people with dementia, with prevalence estimates as high as 97%.
- Impairments in motivation, Interest, Social behaviour and Awareness,
- Mood disorders
- Anxiety
- Agitation
- Impulsivity
- Hallucinations and Delusions

Psychosis in Vascular Dementia

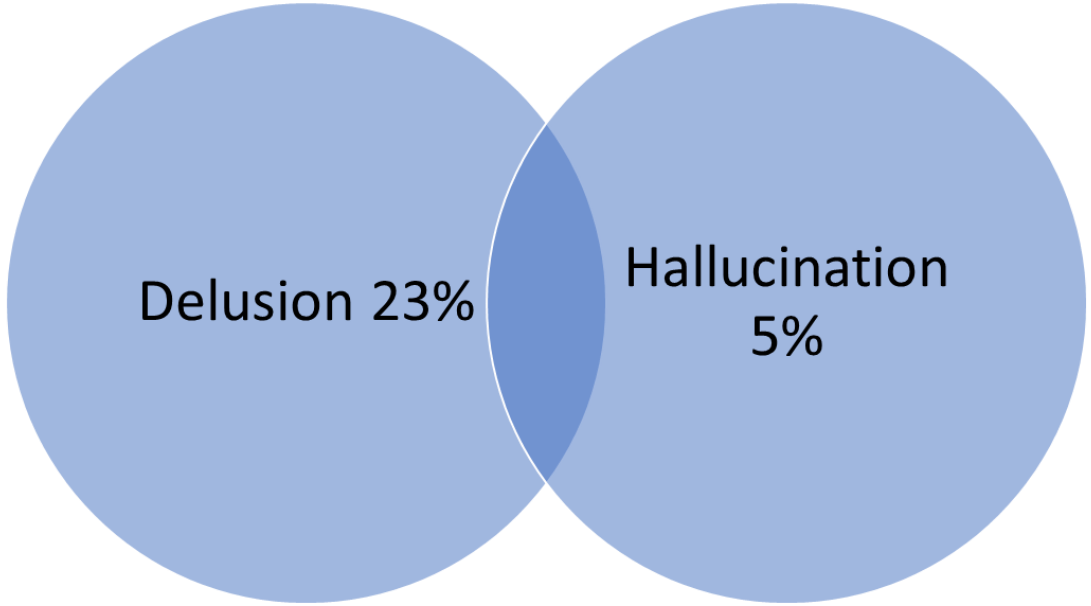
- In VaD, depression and apathy are the most common NPS in VaD.
- Psychotic symptoms may occur, especially in the early stages.
- Hallucinations occur with a similar frequency as is seen in AD,
- Delusions are less common in VaD than in AD.
- VaD rarely occurs in a pure form and the pathology of AD is often present at autopsy in patients diagnosed clinically with VaD.



Psychosis in Alzheimer disease

- In AD, psychosis occurs mostly in the mid-stages of disease
- Delusions are typically paranoid and visual hallucinations are more common than auditory.

- Psychosis in people with AD= 41%
- 23% of participants had delusions only
- 5% had hallucinations only
- 13% had both delusions and hallucinations



- In DLB, delusions are often paranoid, can be very elaborate, and are often related to misidentification.
- In DLB, visual hallucinations, auditory hallucinations, and delusional misidentification increase as cognitive impairment .worsens

- In DLB, nonamnestic cognitive and neuropsychiatric symptoms emerge before motor symptoms(17).
- DLB is characteristically associated with fluctuating cognition and psychiatric and autonomic symptoms.
- In PD, psychotic symptoms change as the disease progresses; patients
- in early stages typically have minor illusions; these progress to hallucinations with insight, followed by hallucinations without insight, and finally to delusions.

- There are several subtypes of frontotemporal lobar degeneration including behavioral variant
- FTD (bvFTD), primary progressive aphasia, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).
- Psychosis with fixed and bizarre delusions may lead to a misdiagnosis of schizophrenia in younger patients. The criteria should accommodate psychosis in all types of NCD.

Associations

Delusion

- older age
- depression
- aggression

Hallucination

- severe dementia
- longer duration of illness
- Greater cognitive and Functional Deficit

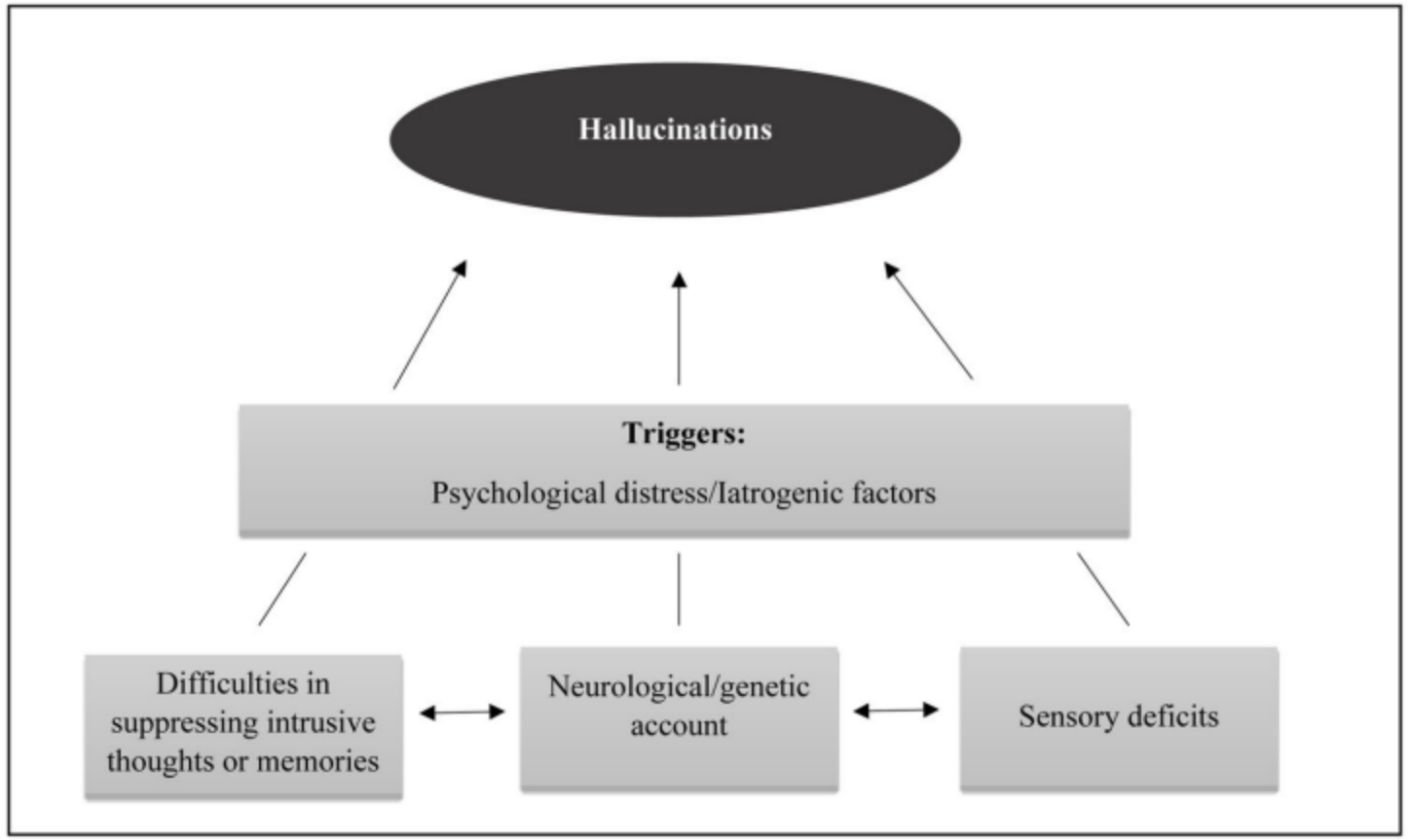


Figure 1.
According to the ALZHA model, hallucinatory experiences in Alzheimer's disease mainly occur in patients with trait markers (i.e., difficulties in suppressing intrusive thoughts or memories, neurological deficits, genetic predisposition and/or sensory deficits), who experience, at a given moment, one or more state markers that will trigger the experience (e.g., psychological distress and/or iatrogenic factors).

Hallucinations

- Hallucinations can manifest in any sensory modality; however, visual and auditory hallucinations are the most common.
- Auditory hallucinations can range from noises to full conversations.
- Visual hallucinations most commonly involve people or animals but can also include faces or deceased individuals, colors, inanimate objects, or unformed images.
- Again, given the overlap between hallucinations and misidentification syndromes, distinguishing between them is not always possible.

Persecutory delusions

- Persecutory delusions, such as delusions of theft, are the most common late-life delusions and occur earlier in the AD course
- Delusions of theft
- Delusions of infidelity or abandonment,
- Beliefs that deceased individuals are alive
- General suspiciousness not related to theft (for example, being plotted against, sent to jail or evicted)
- Elaborate systematized delusions, including erotomania or religiosity.

Misidentification syndromes

- Suggest advanced cognitive impairment, prosopagnosia, impaired self-monitoring, or disruptions in signal processing and/or sensory integration circuitry.
- Beliefs that strangers are residing in one's home (phantom boarder syndrome)
- loved ones have been replaced by impostors
- Images on television are real (TV sign)
- Belief that the person in the mirror is someone else (Mirror signe)

Misidentification syndromes

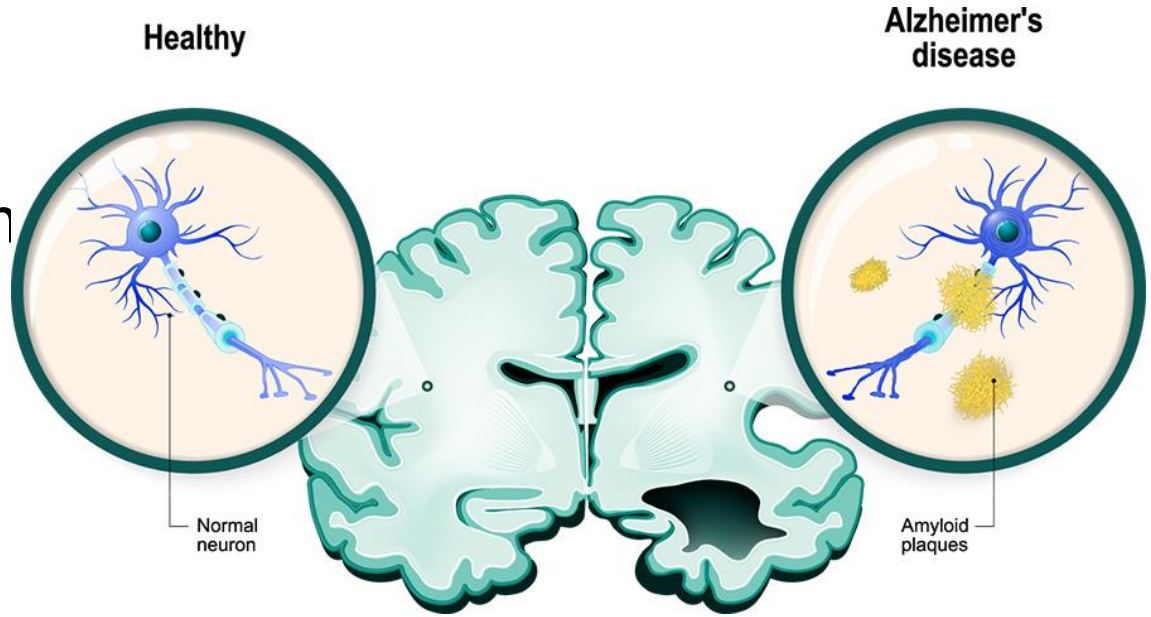
- might suggest advanced cognitive impairment, prosopagnosia, impaired self-monitoring, or disruptions in signal processing and/or sensory integration circuitry

- Distinguishing between delusions and forgetfulness or confabulation requires an appreciation of whether information was encoded into memory:
  - persistence of the belief suggests a delusion,
  - Inconsistent statements are more suggestive of confabulations

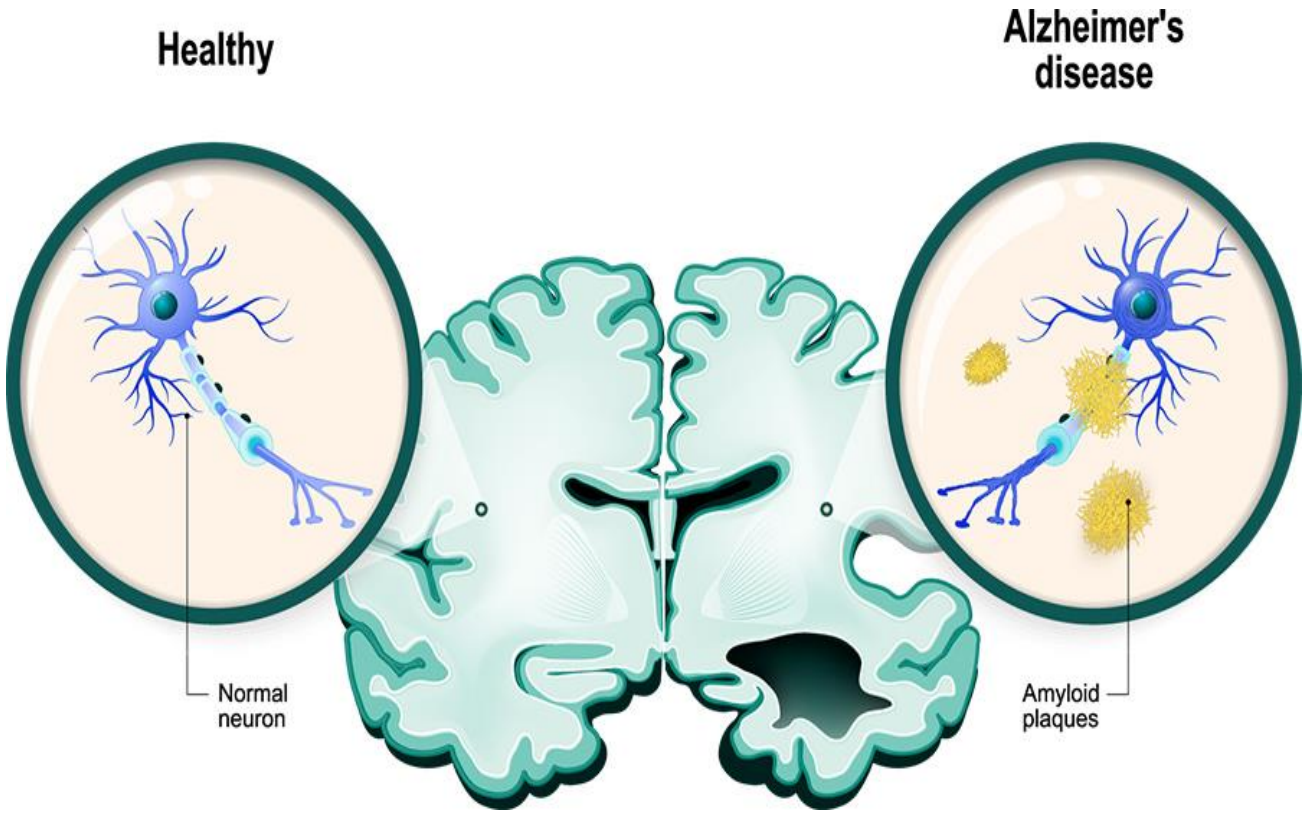
Comorbidities

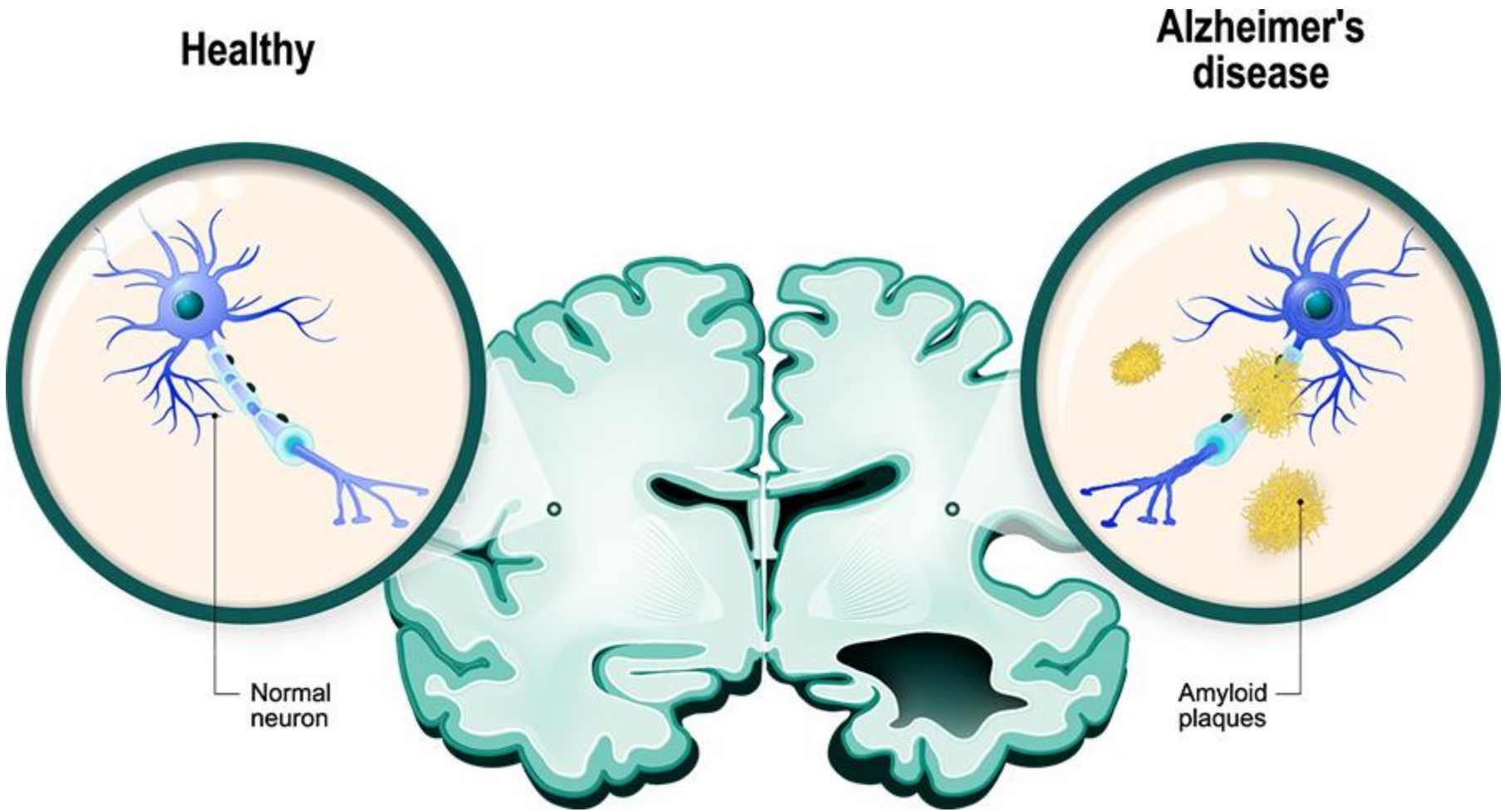
- **Agitation**:
- IPA criteria lies in the description of three domains of agitation which might be used to improve case definitions and to define different treatment targets.
  - verbal aggression
  - physical aggression
  - excessive motor activity
- **Affective symptoms**
- when they co-occur, psychotic and affective symptoms in MCI are associated with a higher risk of incident dementia than either factor alone.

- A modest but statistically significant association between AD psychosis and the APOE ε4 was reported.
- Numerous post-mortem studies have found that psychotic symptoms in AD are associated with an increased burden of NFT pathology and hyperphosphorylated tau.
- Several other studies indicated that associated with psychosis in women

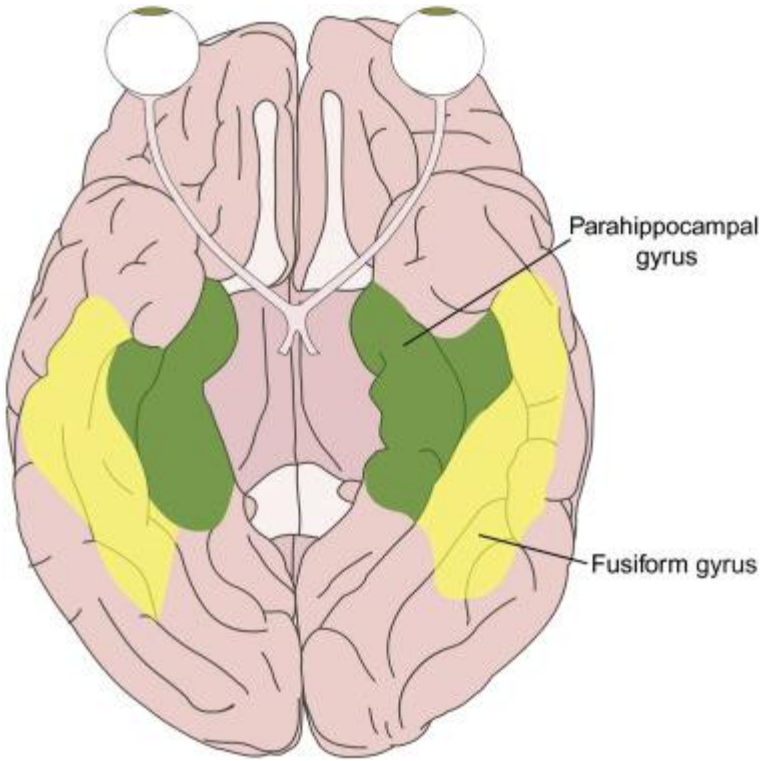


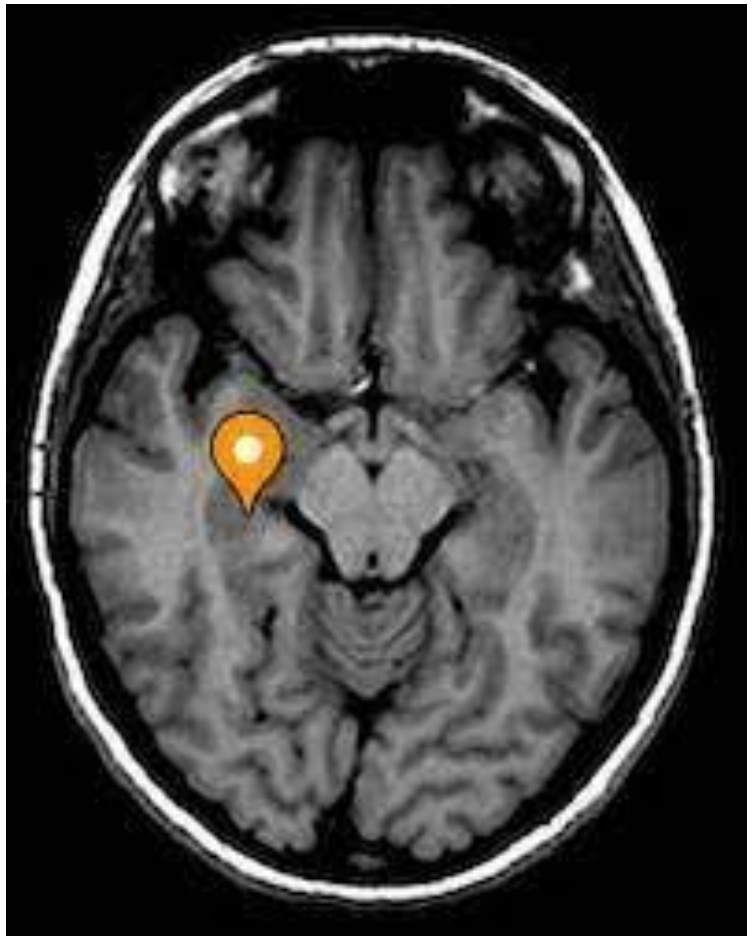
- Although comorbid Lewy body pathology does seem to confer a risk of psychosis in AD, it does not account for all cases.
- Comorbid vascular pathology also seems to be associated with psychotic symptoms in AD.
- The association between leukoencephalopathy and psychosis in AD was replicated in a 12-year longitudinal study.


Healthy
Alzheimer's disease
Normal neuron
Amyloid plaques


Healthy
Alzheimer's disease
Normal neuron
Amyloid plaques

- An analysis of the NACC cohort revealed accelerated atrophy in frontal and temporal lobes in individuals with delusions, and other studies in independent cohorts have reported links with hippocampal and parahippocampal atrophy.
- The parahippocampal atrophy was implicated in delusional misidentifications, consistent with findings from neuropathological studies.
- The most consistent evidence is for right-sided frontal hypometabolism and hypoperfusion in right frontal cortices post hippocampus and bilateral temporal.


Parahippocampal gyrus
Fusiform gyrus



Brain Networks

- The lack of involvement of frontal areas may be surprising but the authors highlight possible links between posterior cortical atrophy and frontal circuits and the default mode network (DMN).
- The DMN is disrupted in AD and other disorders characterized by psychosis. The DMN has been the focus of a number of functional imaging studies in recent years because of the wider literature showing that it is disrupted in AD and other disorders characterized by psychosis.

Frontotempral atrophy delusion

Parital cerebellum atrophy prior to the onset of delusions

DMN dysfunction

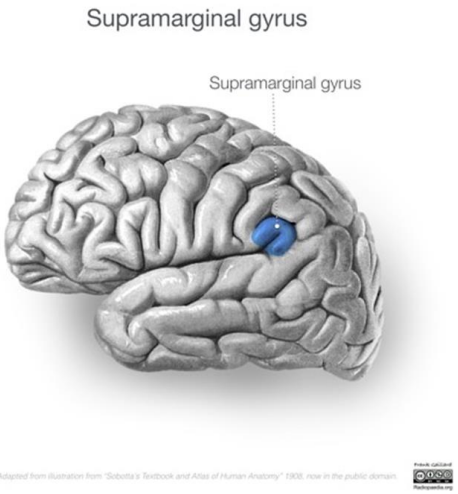
Hippocampus parahippocampal atrophy misidentification delusion

Supramarginal thinning in Parietal lobe hallucination

Another study of Alzheimer's Disease Neuroimaging Initiative (ADNI) data found that cortical thinning in the supramarginal area of the parietal lobe was a risk factor for hallucination

ADNI

- Another study of Alzheimer's Disease Neuroimaging Initiative (ADNI) data found that cortical thinning in the supramarginal area of the parietal lobe was a risk factor for hallucination
- In a longitudinal study, again using the ADNI cohort, reported an increased rate of grey matter atrophy in the cerebellum and parietal lobe prior to the onset of delusions



Functional Imaging

- In the newer SPECT study, regional hypoperfusion was largely confined to the right hemisphere
  - orbitofrontal
  - Inferior temporal gyrus
  - Parahippocampal cortex
  - Posterior insula
  - Amygdala
- bilaterally in the temporal poles

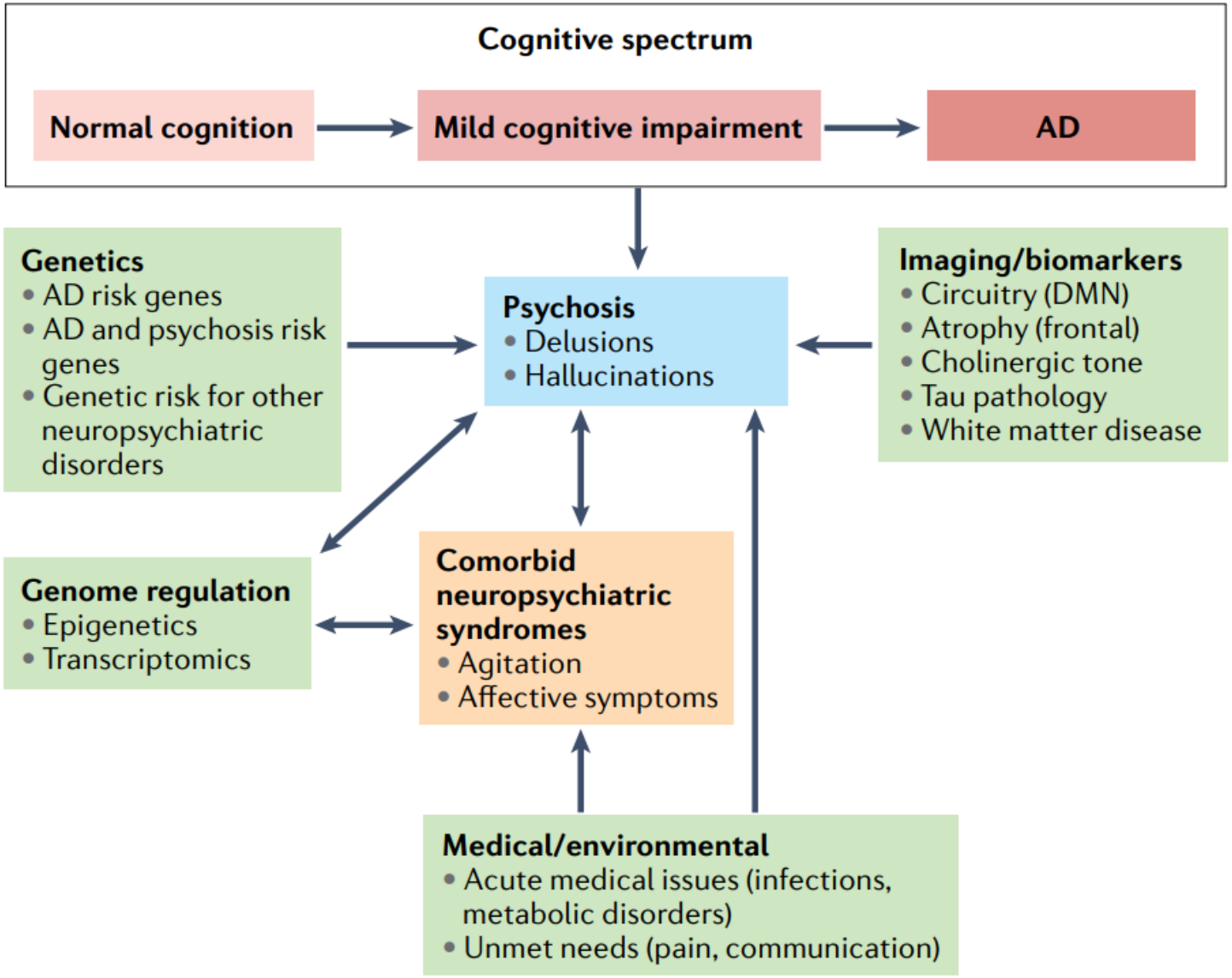


Fig. 2 | **Psychosis in AD: a conceptual model.** Psychosis can emerge across the cognitive continuum in older adults. Before syndromic psychosis can be diagnosed,

Parkinson Disease Dementia

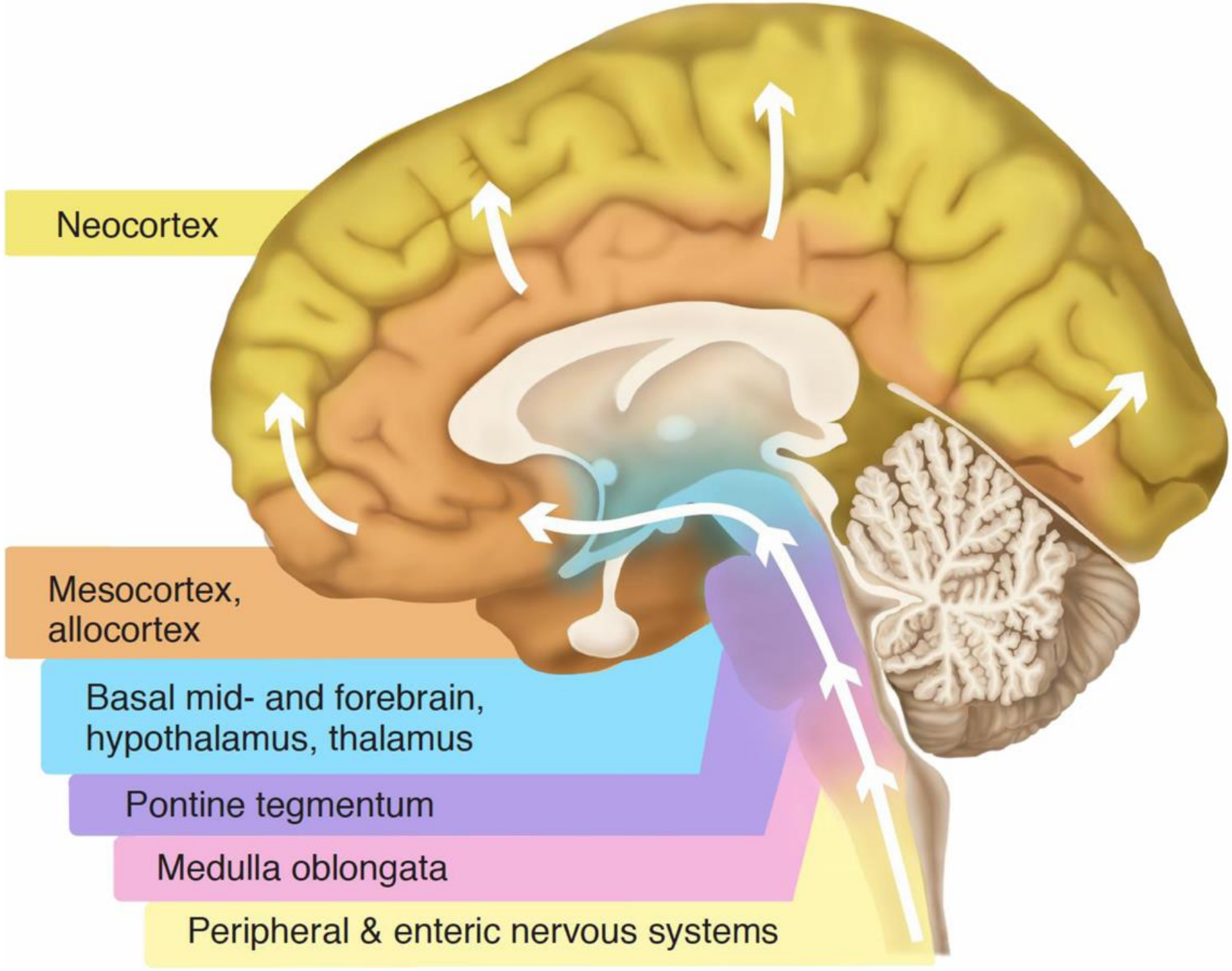
- 1. low-frequency, “pill-rolling” (supination-pronation) hand tremors at rest;
- 2. muscle rigidity during passive movement;
- 3. bradykinesia affecting the initiation and execution of internally generated
- movements;
- 4. loss of postural reflexes, manifesting as postural instability

PD

- Parkinson’s disease (PD) is the second most common neurodegenerative disease seen in older adults after Alzheimer’s disease.
- Parkinson’s disease psychosis (PDP) is a common, non-motor feature of PD, which increases caregiver stress and is a risk-factor for nursing home placement.
- In 2020, an estimated 930,000 individuals in the United States aged ≥45 years suffered from Parkinson’s disease with an expected rise to 1,238,000 by 2030.

PD

- The cardinal motor symptoms of PD :
  - bradykinesia
  - resting tremor
  - rigidity.
- There is a spectrum of psychiatric symptoms that may present in patients throughout the disease course, including but not limited to psychosis.


Neocortex
Mesocortex,
allocortex
Basal mid- and forebrain,
hypothalamus, thalamus
Pontine tegmentum
Medulla oblongata
Peripheral & enteric nervous systems

LOCATION OF STAGES

Stage 1 - Peripheral and enteric nervous system

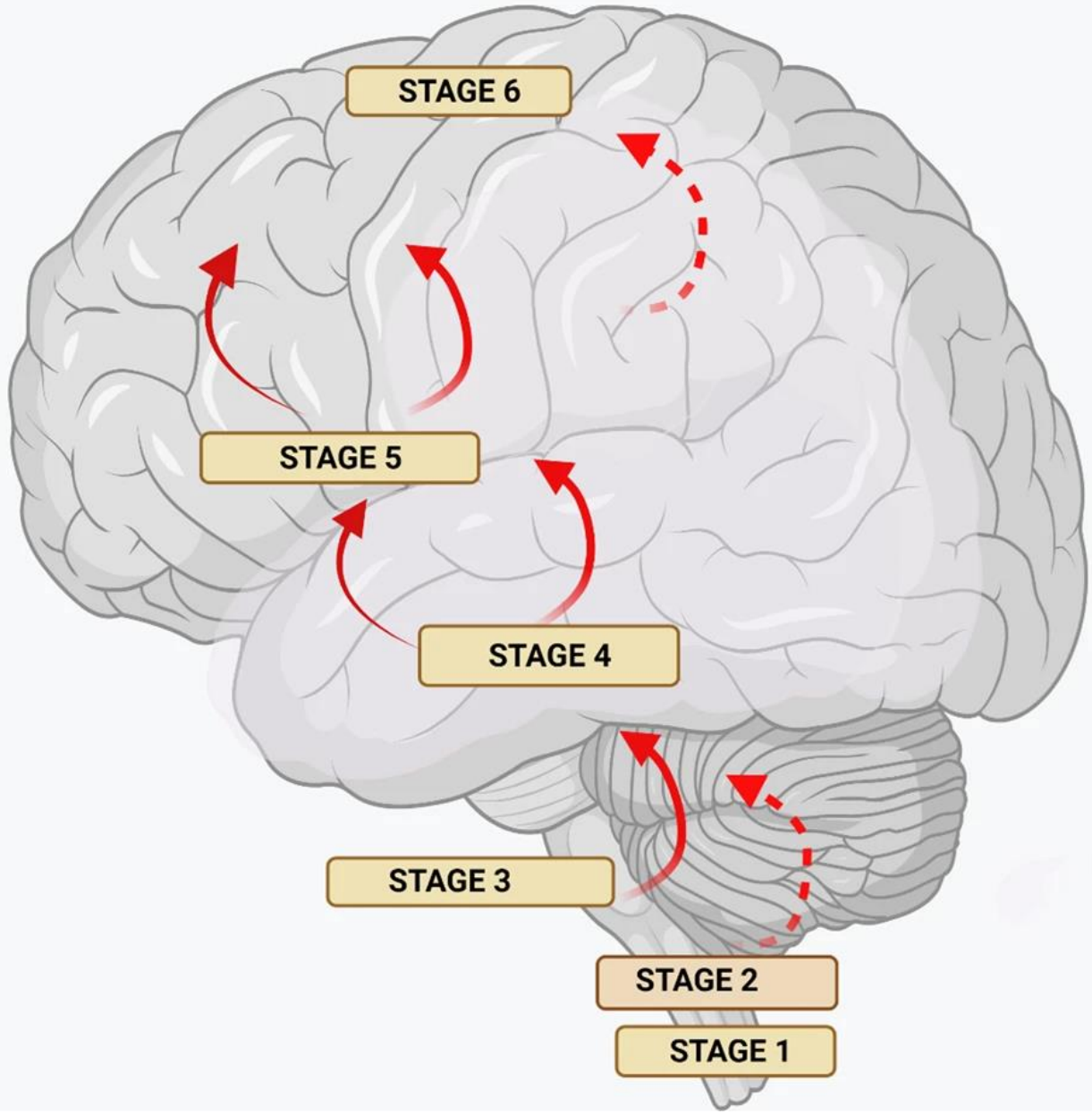
Stage 2 - Medulla Oblongata

Stage 3 - Pontine tegmentum

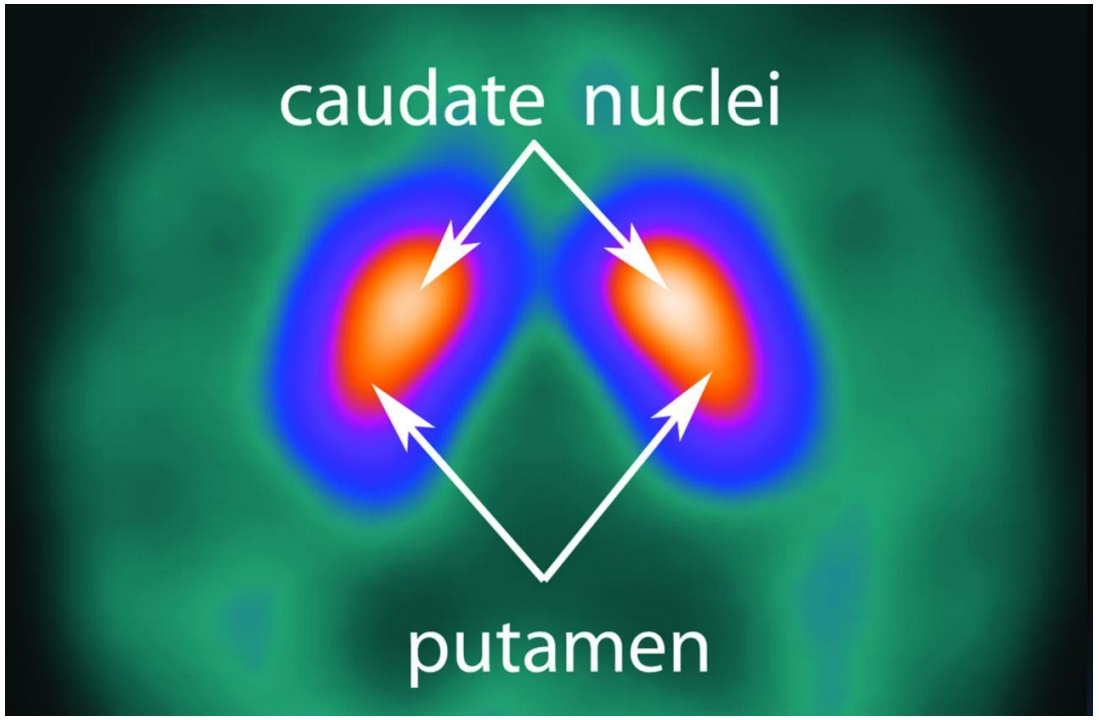
Stage 4 - Basal, mid, and fore-brain, hypothalamus, thalamus

Stage 5 - Mesocortex, allocortex

Stage 6 - Neocortex



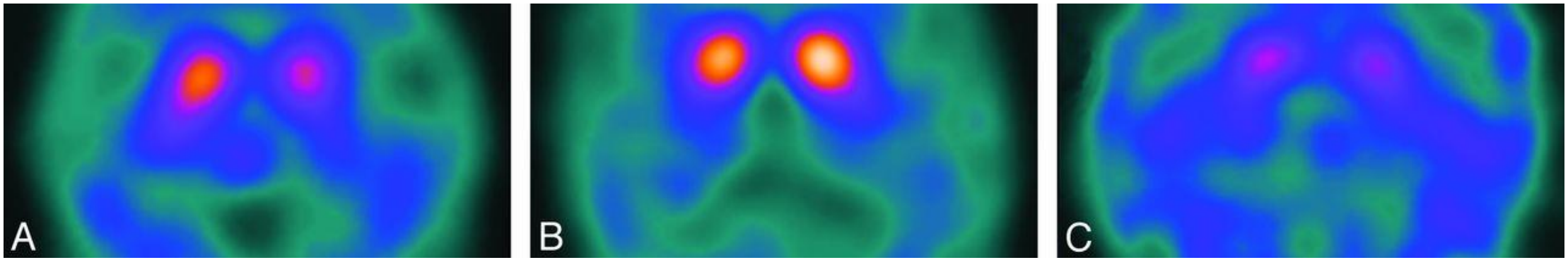
- DaT Scan (DaT scan or Dopamine Transporter Scan) commonly refers to a diagnostic method, based on SPECT imaging, to investigate if there is a loss of dopaminergic neurons in striatum
- DaTSCAN is indicated in cases of tremor when its origin is uncertain. Although this method can distinguish essential tremor from Parkinson's syndrome, it is unable to distinguish between Parkinson's disease, Dementia with Lewy bodies, Parkinson's disease dementia,[3] multiple system atrophy or progressive supranuclear palsy

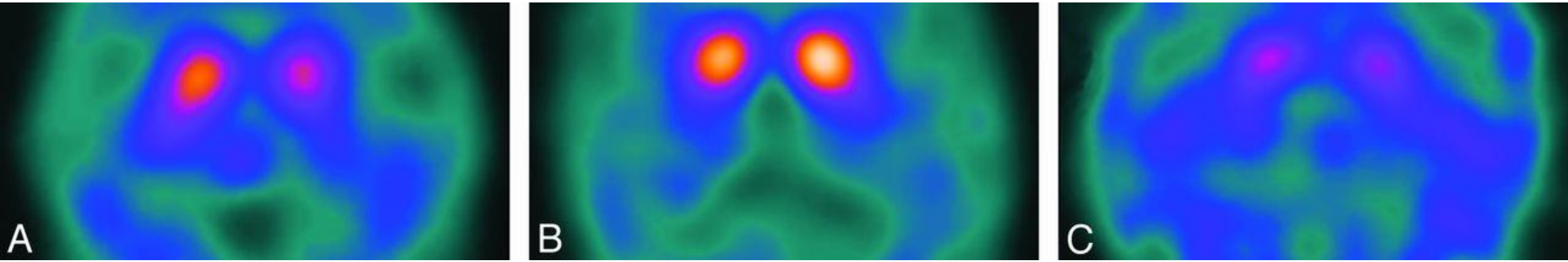


- Normal study findings. The axial 123I-FP-CIT DaT-SPECT image demonstrates symmetric tracer uptake in the caudate nuclei and putamina, with very low-grade, almost absent, background activity.

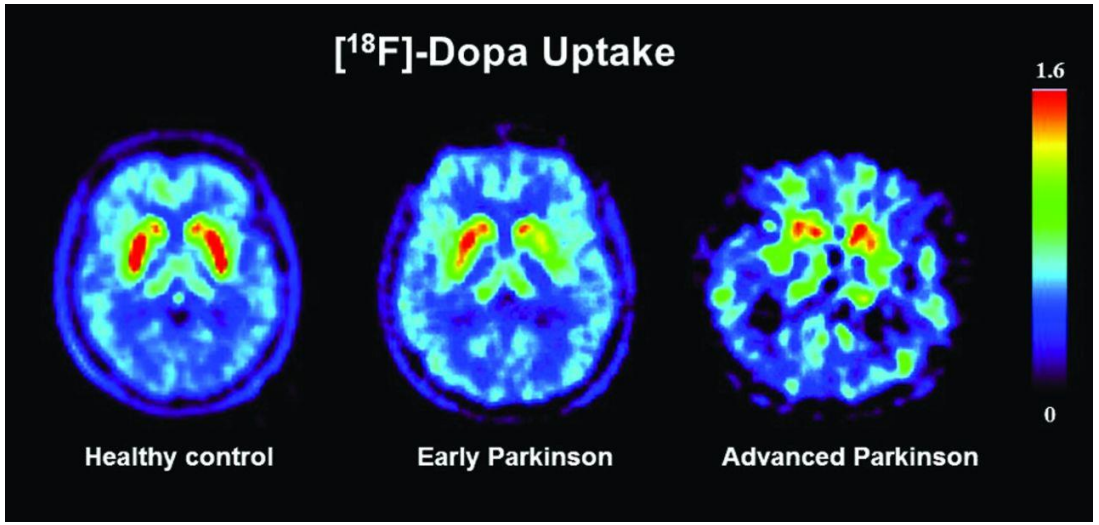
The Role of Functional Dopamine-Transporter SPECT Imaging in Parkinsonian Syndromes.American journal of Neuroradiology.2015

- The Role of Functional Dopamine-Transporter SPECT Imaging in Parkinsonian Syndromes

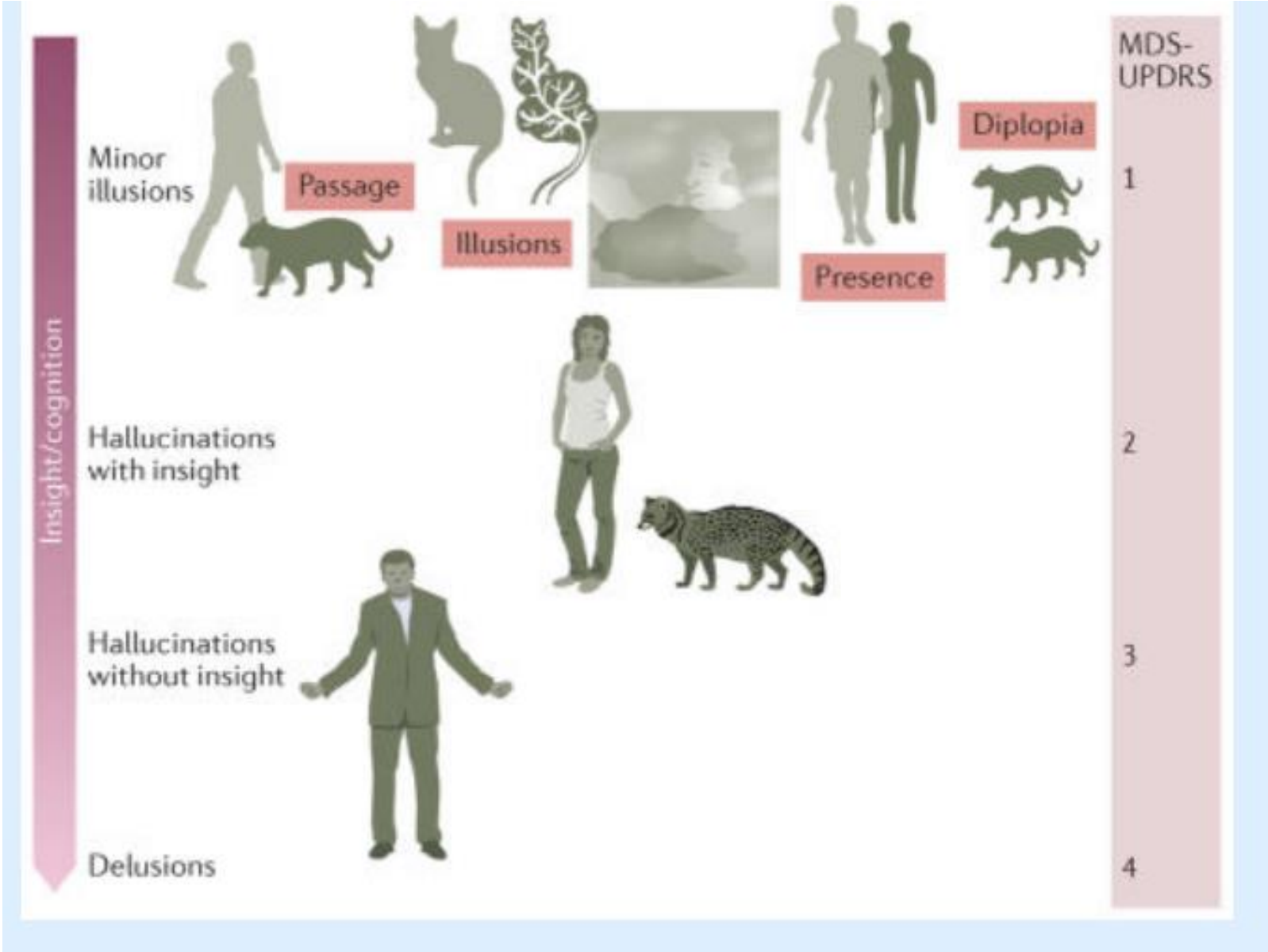

A
B
C



Axial 123I-FP-CIT DaT-SPECT sections depicting the different patterns of abnormality seen in PD as described by Catafau and Tolosa2—type 1: asymmetric activity with reduced putaminal uptake in 1 hemisphere (A); type 2: symmetric reduction in putaminal uptake in both hemispheres (B); and type 3: virtual absence of uptake in the putamina and caudate nuclei despite high gain as demonstrated by ample background activity (C).



- Axial 18F-DOPA PET images through the striatum. The patient with early Parkinson disease shows an asymmetric reduction in putaminal radiotracer uptake. With further disease progression, both putamina show a substantial reduction in radiotracer uptake.



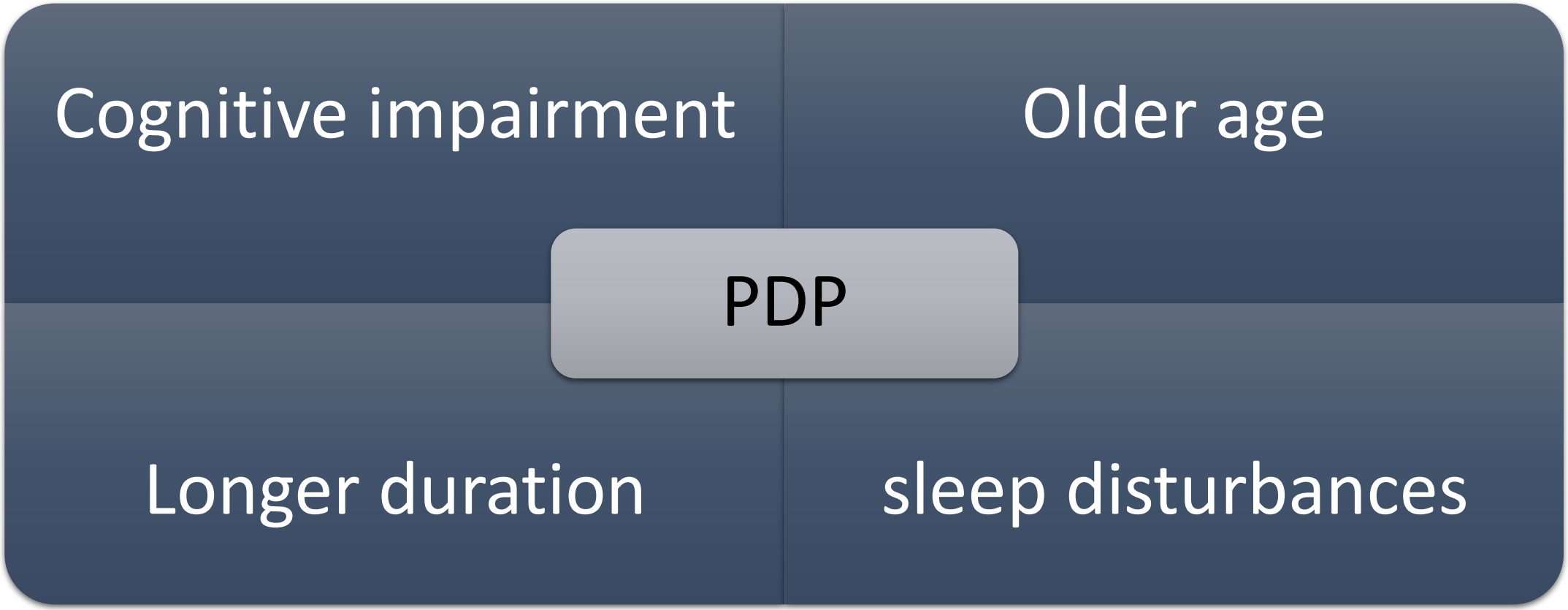
The psychosis spectrum in Parkinson’s disease. Nat Rev Neurol. 2017 February

The prevalence of PDP

- Minor phenomena such as sense of presence and visual illusions have
- been reported to impact 17 to 72% of patients
- The lifetime risk of visual hallucinations can reach up to 50%.
- Less commonly reported symptoms include auditory hallucinations,
- tactile hallucinations, and delusions.
- It is estimated that up to 60% of PD patients will develop psychosis within 12 years of onset.

- Dementia and cognitive impairment are 2 key independent risk factors for hallucinations.
- There is a 6-fold increase in likelihood of patients with PD developing dementia within their lifetime when compared to healthy individuals.
- 70% of PD patients with dementia experienced hallucinations compared to 10% of patients with intact neurocognitive function
- Older age of onset and longer duration of PD are 2 additional risk factors associated with the incidence of hallucinations
- Disease duration being an independent predictor of visual hallucinations.

risk factors associated with the incidence of hallucinations



Nature of Psychotic Symptoms in PDP

- Minor hallucinations :
- Presence Hallucination:
- presence or the sense that another person or animal is nearby.
- Passage hallucinations which are brief hallucinations in one's periphery.
- Presence and passage hallucinations are more likely to occur indoors and upon waking up from sleep.
- visual illusions that are defined as misperceptions of real external stimuli.
- Minor hallucinations can precede the development of motor symptoms of PD or complex visual hallucinations.
- Other forms of hallucinations including auditory, tactile, and olfactory occur with less frequency. They are often associated with older age and occur in conjunction with visual hallucinations.

Nature of Psychotic Symptoms in PDP

- Simple visual hallucinations can present as flashes of light or blurry colors.

- Complex visual hallucinations consist of defined visualizations of persons, animals, or objects.
- The content of complex hallucinations can vary in familiarity, color contrast, and distortion.
- Complex hallucinations are more common with increased duration of PD and can last several seconds to minutes.
- For example, a patient may visualize a family pet that died years prior or bugs crawling on the walls.
- Both types of visual hallucinations occur most commonly in poor lighting situations such as during sunset or when waking up from sleep.

- The dogma is that overstimulated meso-cortico-limbic dopamine receptors cause PDP.
- This overstimulation is caused by dopaminergic-serotonergic interactions.
- First, Lewy bodies composed of alpha-synuclein disrupt dopamine and serotonin transmission by depositing in the substantia nigra and cerebral cortex.
- High Lewy body densities in the amygdala and parahippocampal cortex are associated with visual hallucinations.
- Cortical serotonin 5-HT2A receptors are subsequently upregulated and overstimulated, with activity in the temporal cortex and visual pathways proposed as the cause of visual hallucinations.
- The upregulated receptors located in the prefrontal cortex then affect projections to the ventral striatum that regulate dopamine release.


PMED

Table 2. Differences between psychosis of dementia and schizophrenia.[33,34,36,37]

Features	Psychosis of dementia	Schizophrenia
Prevalence	15–78% of patients	<1% of general population
Bizarre or complex delusions	Rare	Frequent
Misidentification	Frequent	Rare
Common form of hallucination	Visual	Auditory
Schneiderian First rank symptoms *ABCD:Auditory hallucinations, Broadcasting of thought, Controlled thought (delusions of control), Delusional perception*	Rare	Frequent
Past history of psychosis	Rare	Common
Eventual remission of psychosis	Frequent	Uncommon
Need for maintenance antipsychotic therapy	Uncommon	Common

Table 3. Differences between delirium, AD, LBD, and depression.[9–11,37]

Characteristics	Delirium	AD	LBD	Depression
Presenting symptoms	Unfamiliarity with the environment with short term memory loss; "confusion"	Short term memory loss	Motor symptoms may appear before cognitive impairment; fluctuating cognition, visual hallucinations, and REM-sleep behavior disorder are part of core clinical features	Subjective complaints of poor memory and concentration
Onset	Sudden	Insidious	Insidious	Recent
Alertness	Fluctuating	Normal except in late phases	Fluctuating	Preserved
Duration	Hours to weeks	Months to years	Months to years	Variable
Orientation	Disorientation with onset	Disorientation occurs late in course	Fluctuating	Intact
Hallucinations	From onset	May occur late in course	From onset; visual hallucinations well-formed	Could occur in depression with psychotic features
Cognitive functioning	Fluctuating with alertness	Progressive deterioration	Progressive deterioration	Initially intact with efforts to perform cognitive tasks. May deteriorate without treatment progression
Mood	Fluctuate	Labile	Labile	Usually sad
Sundowning	Present	Present	Present	Absent, mood improve as day progress
Course	Usually reversible with treatment	Irreversible with progressive deterioration	Irreversible with progressive deterioration	Completely reversible

attention, executive function, and visuoperceptual ability may be prominent.

- **Core clinical features** (The first 3 typically occur early and may persist throughout the course)

  • Fluctuating cognition with pronounced variations in attention and alertness

  • Recurrent visual hallucinations that are typically well formed and detailed

  • Rapid eye movement (REM) sleep behavior disorder (RBD), which may precede cognitive decline

  • One or more spontaneous cardinal features of parkinsonism: bradykinesia, resting tremor, or rigidity

- **Supportive clinical features**

  Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, or urinary incontinence); hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; and apathy, anxiety, and depression

- **Indicative biomarkers**
  - Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT/PET
  - Abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy
  - Polysomnographic confirmation of REM sleep without atonia
- **Supportive biomarkers**

  A relative preservation of medial temporal lobe structures on CT/MRI scan; generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging; prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Probable DLB

a. Two or more core clinical features are present, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers

Possible DLB

a. Only one core clinical feature, or

b. One or more indicative biomarkers is present, but there are no core clinical features

DLB is less likely

a. In the presence of any other physical illness or brain disorder, including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or

b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.

DLB and PDD

DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term PDD should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting, the term that is most appropriate to the clinical situation should be used, and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

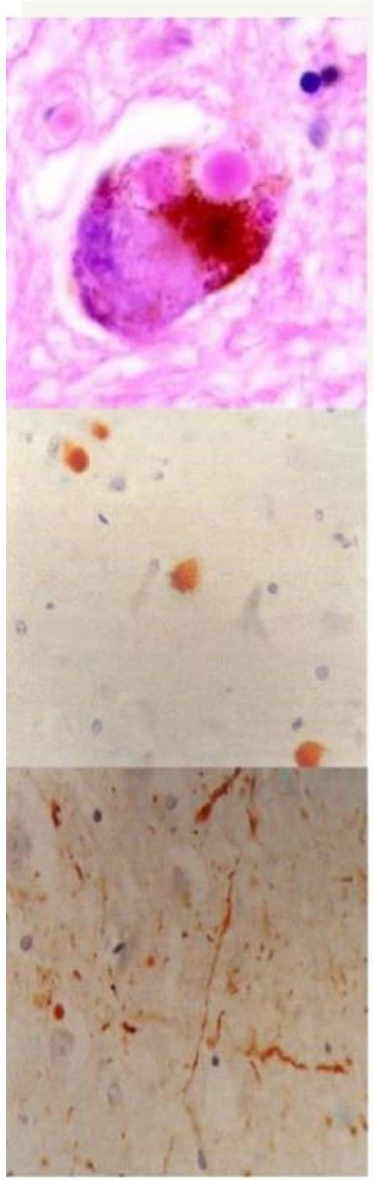
- Psychosis is also a key presenting symptom of DLB.
- Patients with DLB are more likely to present with visual hallucinations and delusions than PD patients with or without dementia.
- .22 Furthermore, DLB is
- caused by deposition of Lewy bodies in the temporal lobe and
- amygdala, and decreased uptake in parts of the visual cortex
- with brain perfusion imaging.23 These changes may account for
- the frequent visual hallucinations which are seen in DLB.

- Psychosis can be present in PD and other neurodegenerative diseases such as Alzheimer's disease (AD) and dementia with Lewy Bodies (DLB).
- The presenting symptoms are also similar between the 3 groups.
- However, in PDP the presence of hallucinations is associated with increased severity of motor systems

- Psychosis in AD is most likely to present with delusions rather than the hallucinations most commonly seen in PDP.
- Psychotic symptoms in FTD are less common. Compared to PD, delusions tend to occur at a higher frequency in patients with FTD.
- Negative psychotic symptoms are also the most common presentation of psychosis in behavioral-variant FTD

- Furthermore, DLB is caused by deposition of Lewy bodies in the temporal lobe and amygdala, and decreased uptake in parts of the visual cortex with brain perfusion imaging.
- These changes may account for the frequent visual hallucinations which are seen in DLB.

Lewy Body Disease



Parkinson's Disease (PD)

Mild Cognitive Impairment

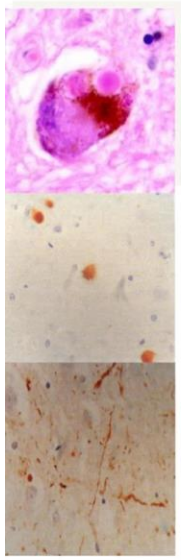
PD Dementia

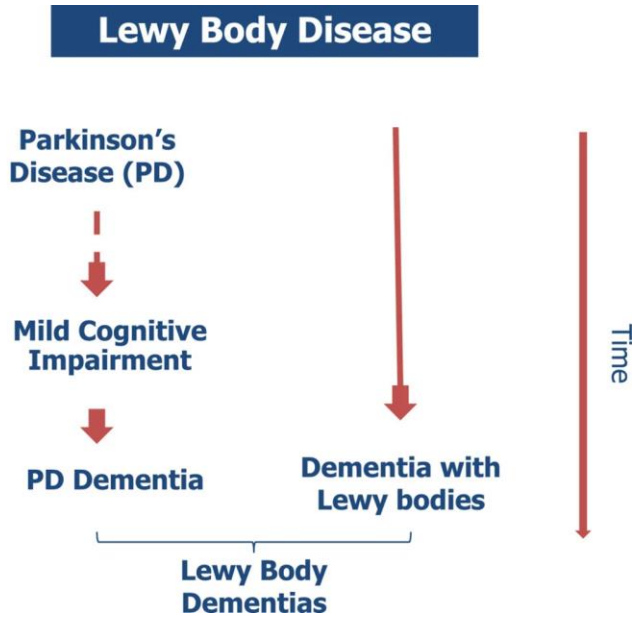
Dementia with Lewy bodies

Lewy Body Dementias

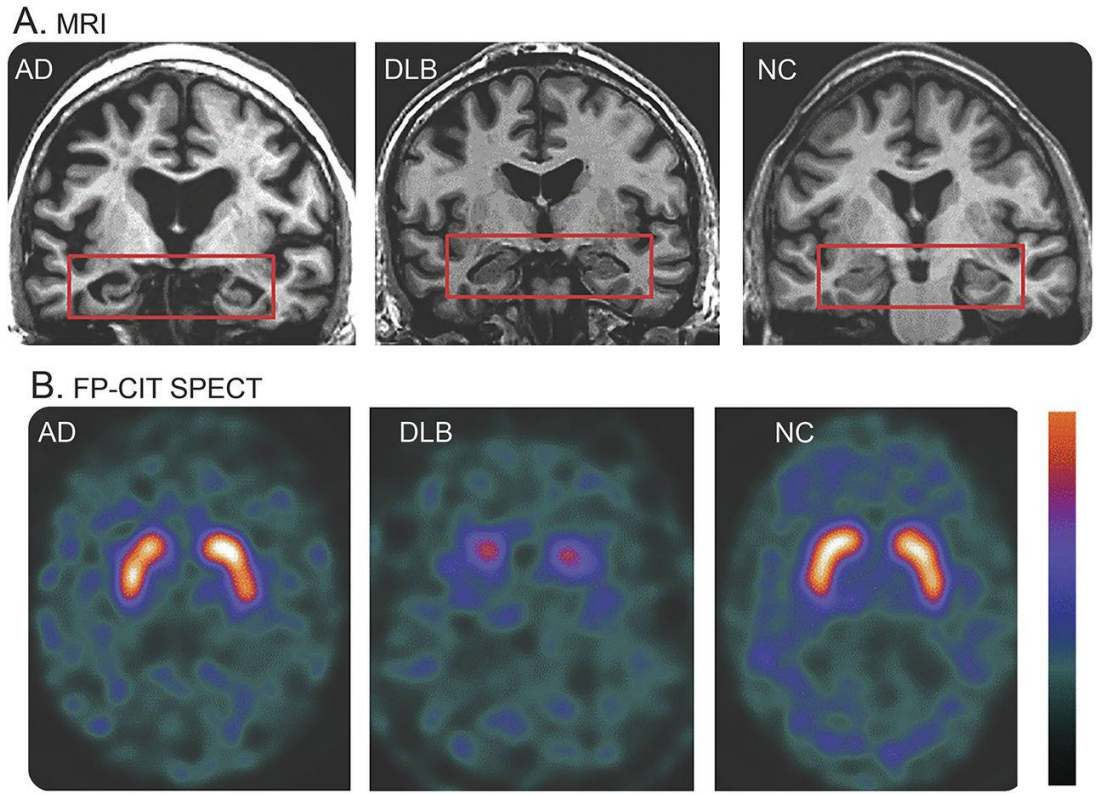
Time

Lewy body diseases (LBDs)





Disease	brain region affected at early stage	Function controlled	symptoms
DLB	Cerebral cortex (outer layer of the brain)	Cognition	Dementia
PD	Substantia nigra (mid brain)	Motor	Movement problems
PDD	Both	Both	Both

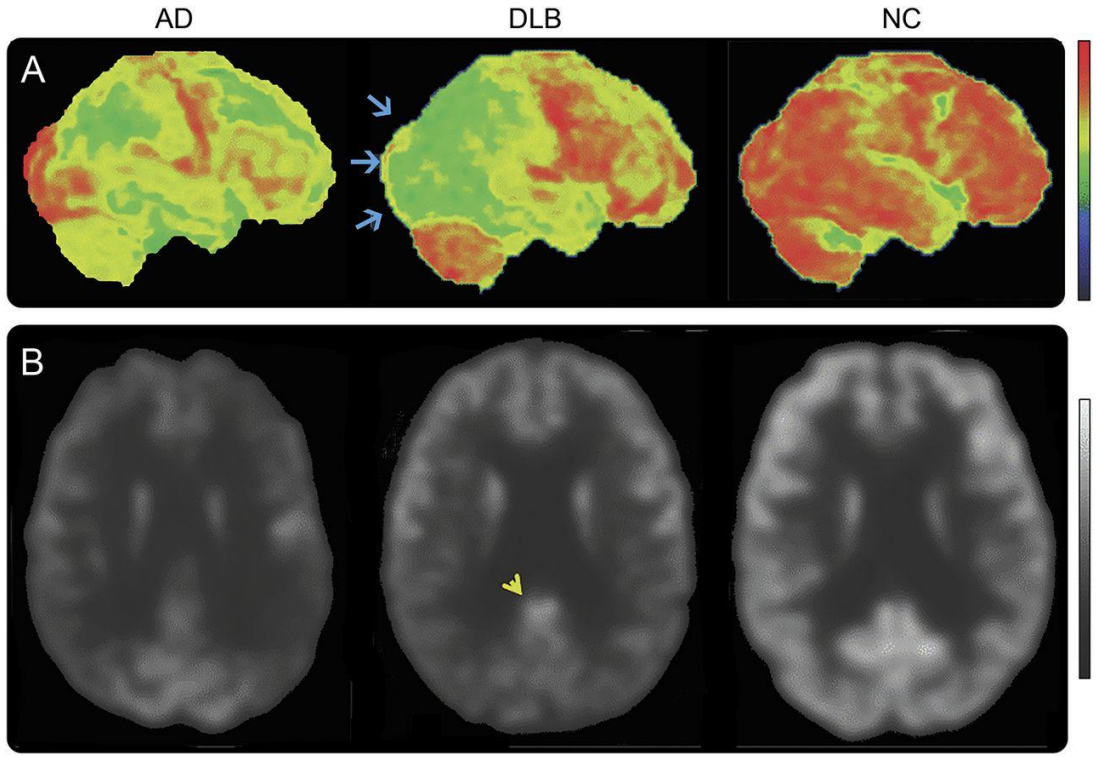


(A) On the MRI, note the relative preservation of medial temporal lobe volume (rectangles) in DLB, which is similar to NC, whereas atrophy is obvious in AD. (B) On the FP-CIT SPECT images, note the minimal uptake in DLB, which is restricted to the caudate (period or full-stop appearance) compared to the robust uptake in the caudate and putamen in AD and NC (comma appearance). Reproduced with permission from Dr. Val Lowe, Mayo Clinic, Rochester, MN.

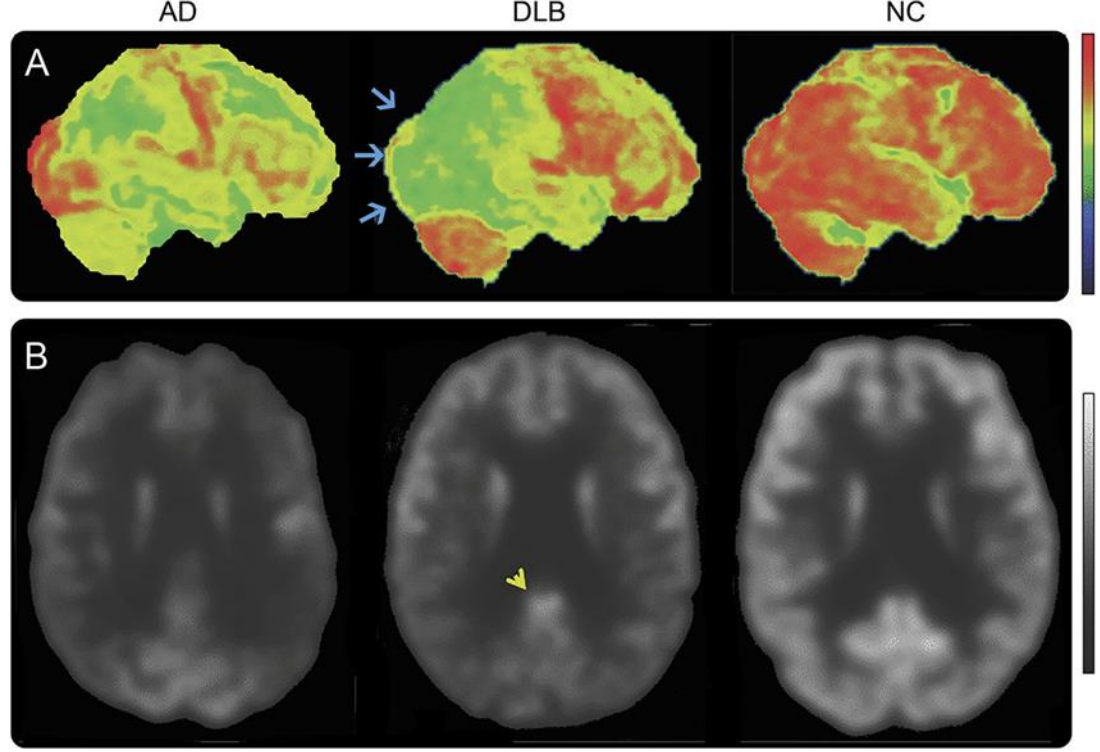
Figure 1 Coronal T1-weighted MRI and ^{123}iodine FP-CIT SPECT images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)

Diagnosis and management of dementia with Lewy bodies.American academy of

Figure 4 18F-FDG-PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)



(A) Right lateral metabolic surface map projection. (B) Standard axial view transecting the posterior cingulate region. Occipital lobe metabolism is preserved in AD and NC but reduced (blue arrows) in DLB. Hypometabolism in AD is predominantly in the temporal, parietal, and frontal regions. There is normal metabolism as reflected by the normal ^{18}F-FDG uptake (lighter shade of gray) in the posterior cingulate region (yellow arrowhead) surrounded by reduced ^{18}F-FDG uptake (darker gray) in the adjacent occipital cortex in DLB, representing the cingulate island sign. This contrasts with the relatively reduced ^{18}F-FDG uptake in the posterior cingulate and relatively preserved ^{18}F-FDG uptake in the occipital cortex regions in AD. In the control, there is normal ^{18}F-FDG uptake in the posterior cingulate, occipital, and other neocortical regions. Color and grayscale sidebars show increasing degrees of deviation from normal as the signal trends lower in the sidebars (red is normal while black is maximally abnormal in color images; white is normal while black is maximally abnormal in grayscale images). Reproduced with permission from Dr. Val Lowe, Mayo Clinic, Rochester, MN.



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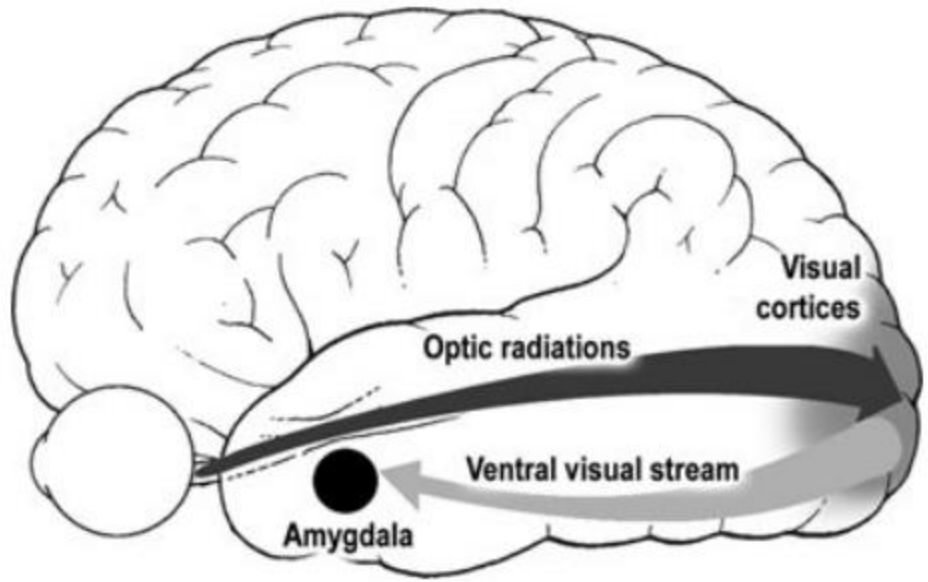


Fig. 2 Diagram of the major visual pathways implicated pathologically in VH in PD.

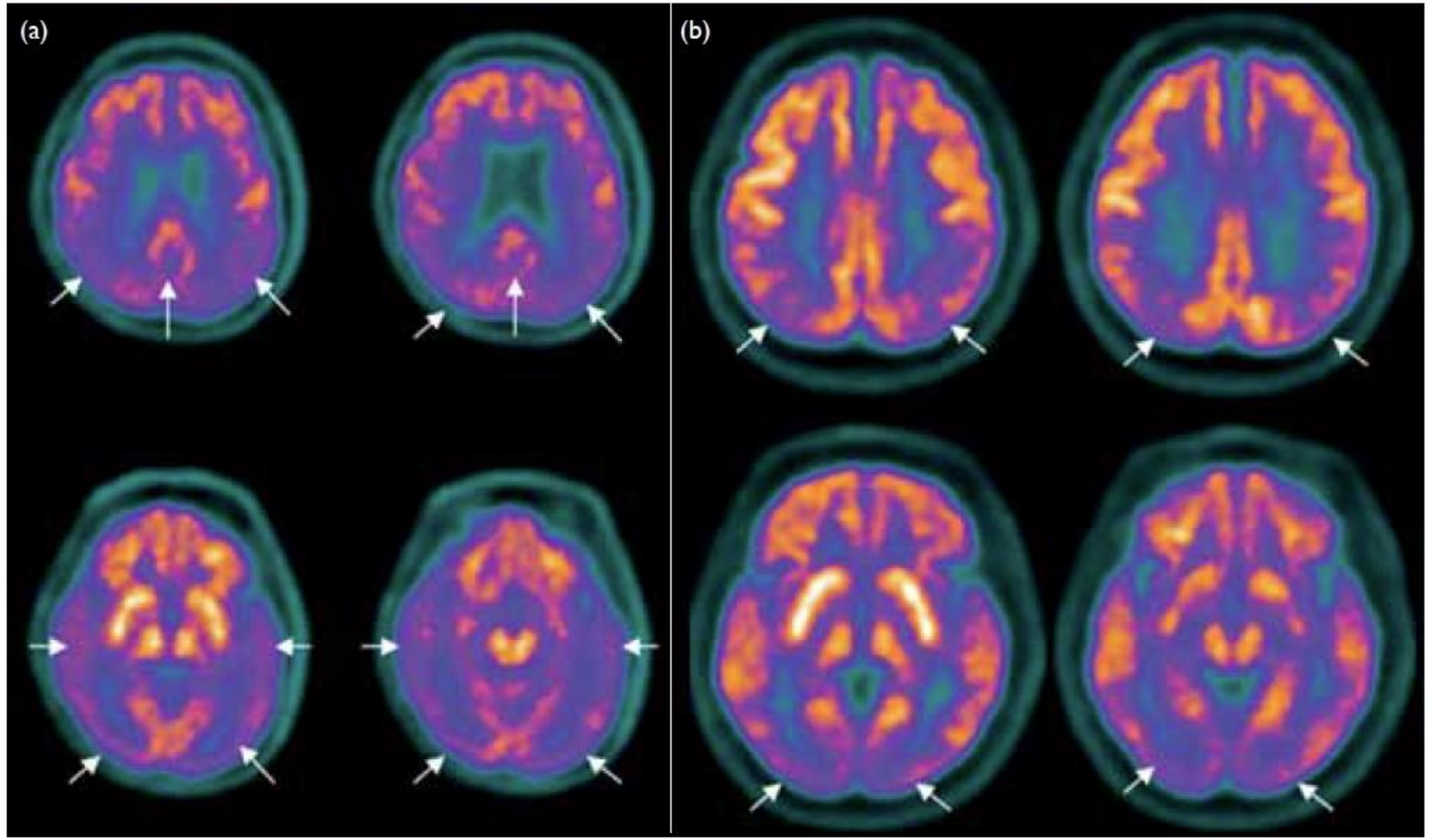
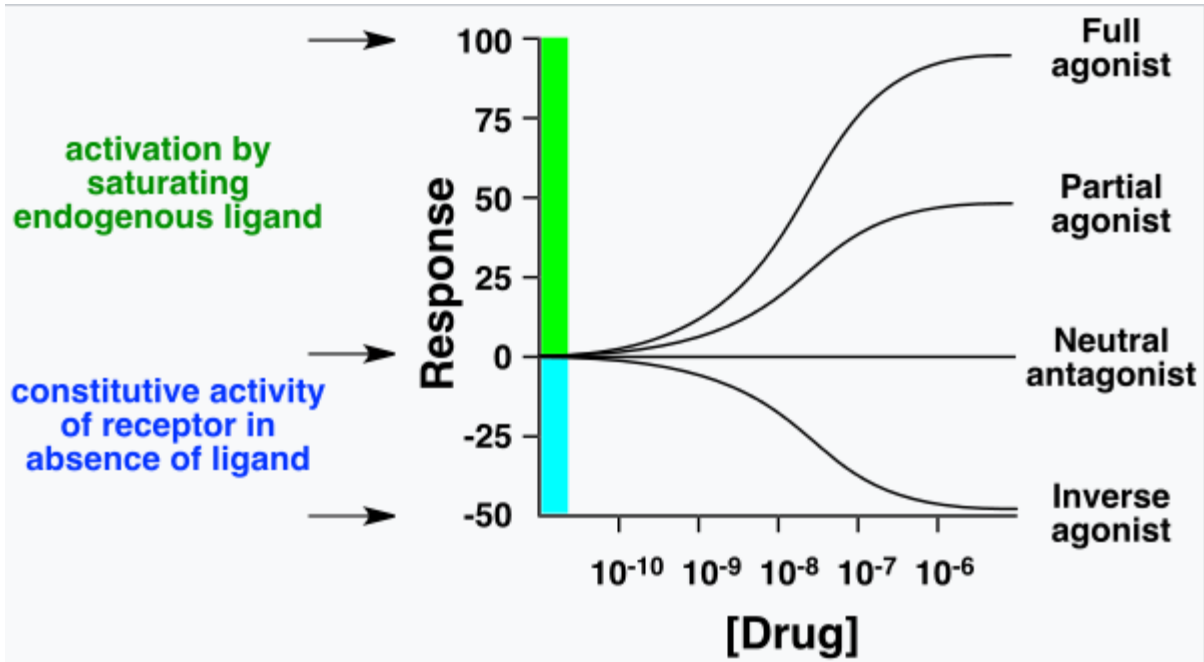


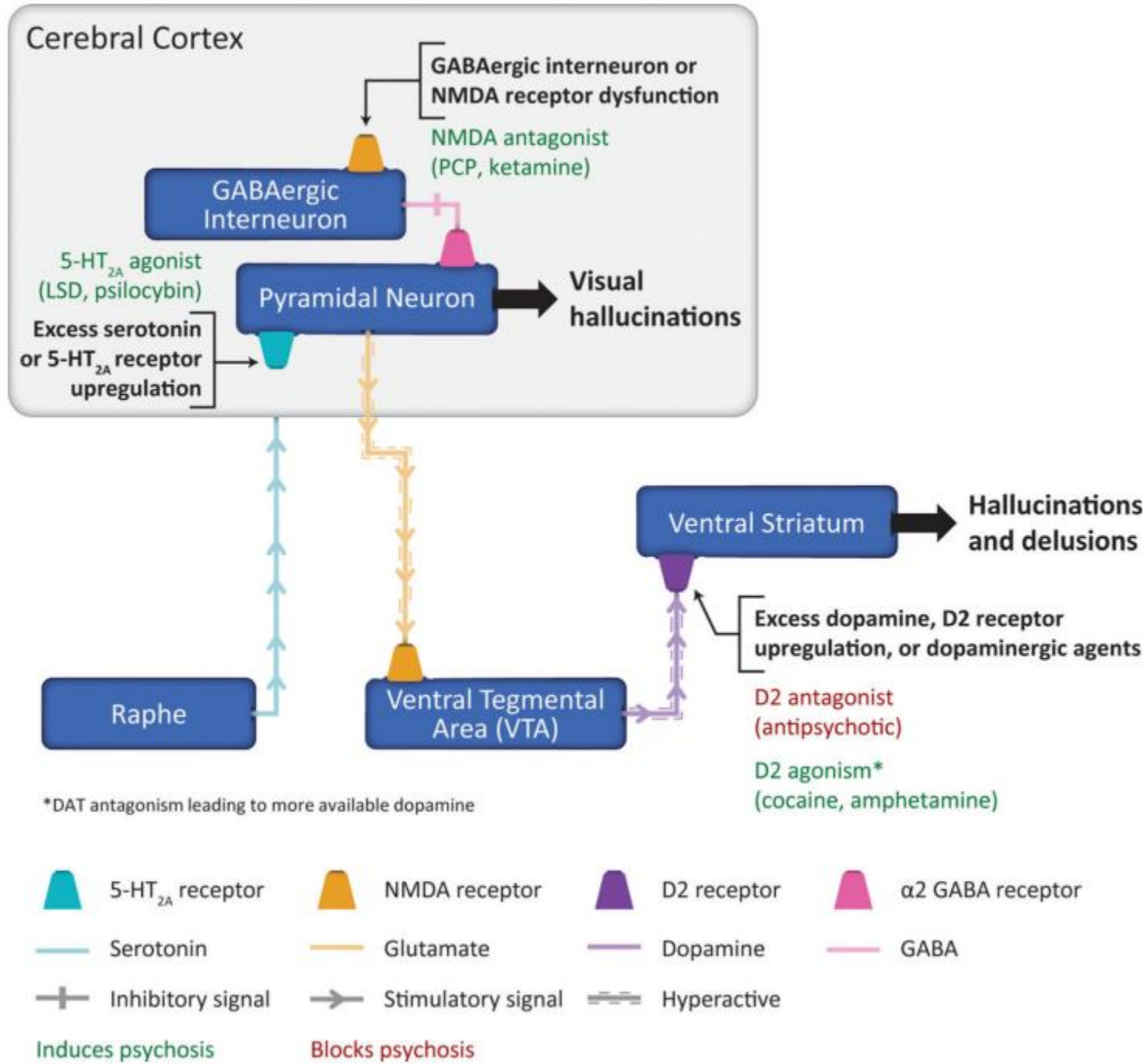
FIG. ^{18}FDG-PET brain imaging of patients with LBD

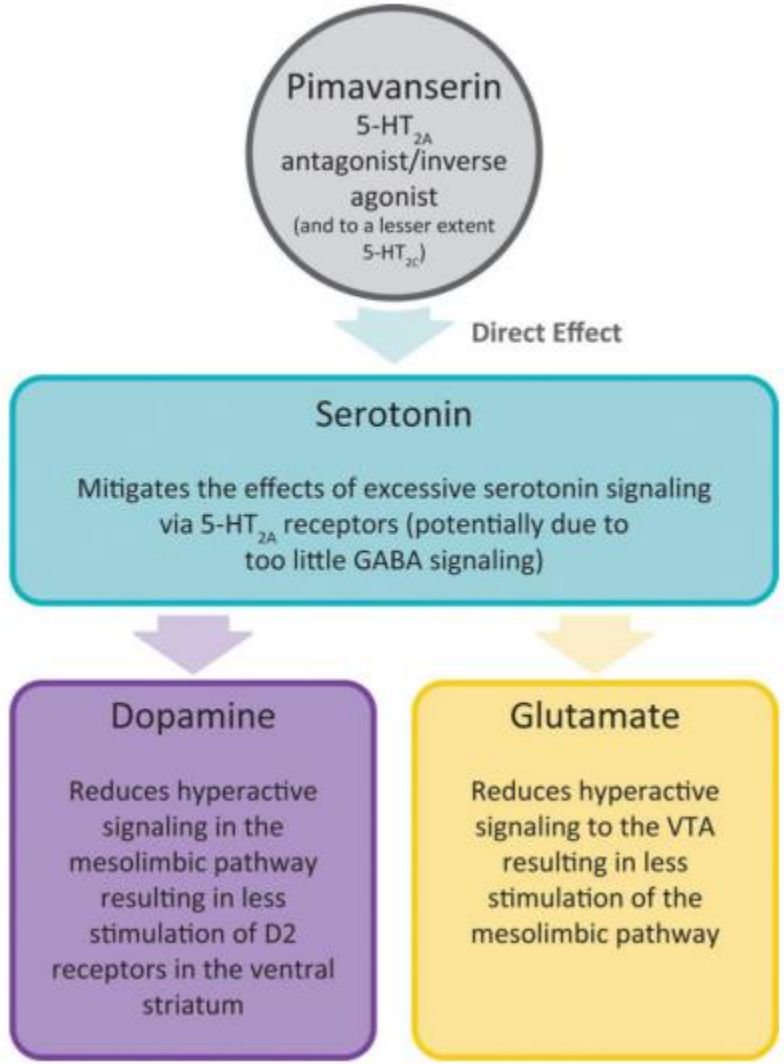
(a) A patient with an AD pattern of hypometabolism over the bilateral temporoparietal and occipital lobes and posterior cingulate gyrus (arrows). (b) A patient without an AD pattern of hypometabolism; the hypometabolism occurred in mainly bilateral occipital lobes and mild hypometabolism over the bilateral parietal lobes (arrows)

Abbreviations: AD = Alzheimer's disease; ^{18}FDG-PET = [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography; LBD = Lewy body dementia



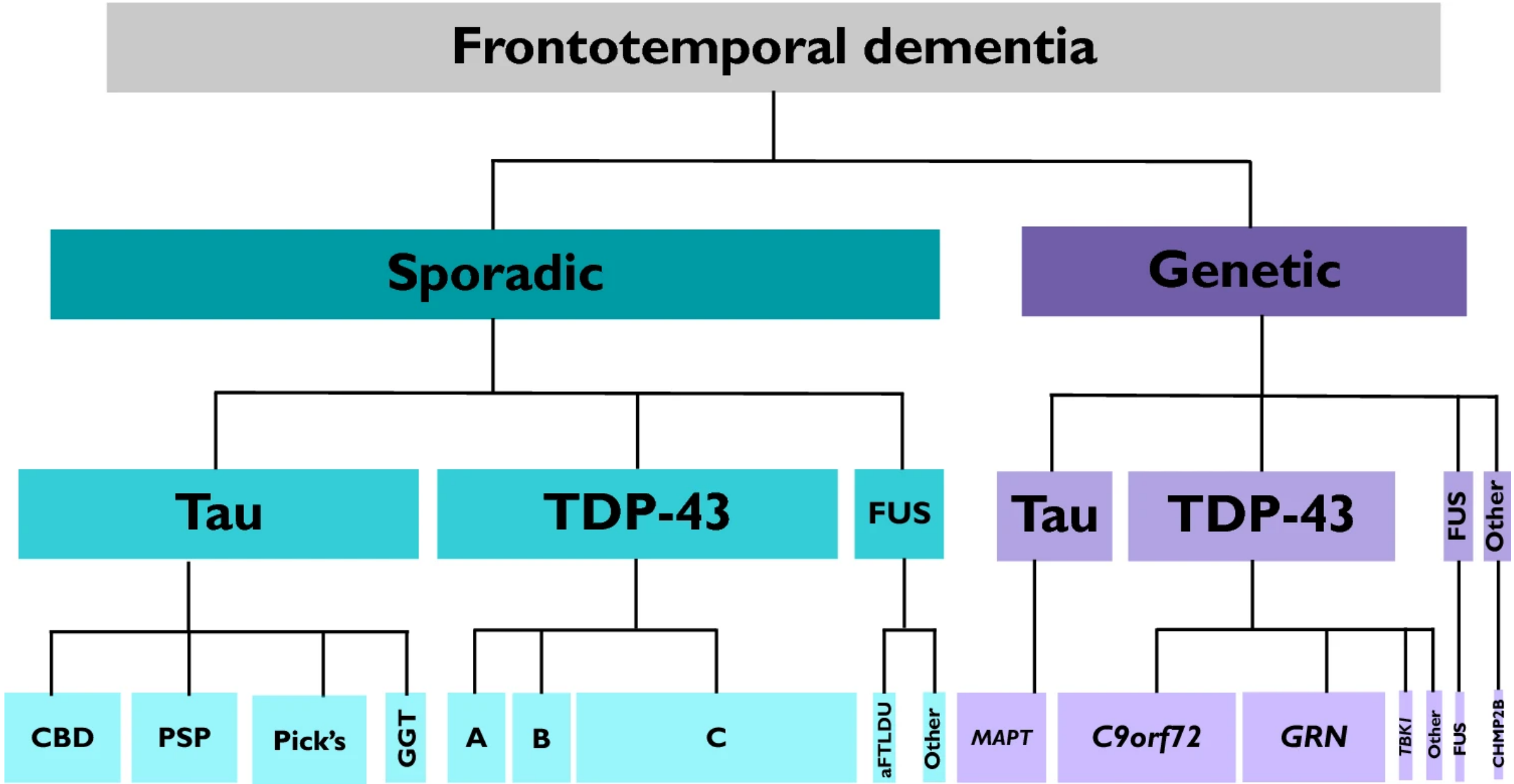
Dose response curves of a full agonist, partial agonist, neutral antagonist, and inverse agonist


Cerebral Cortex
GABAergic interneuron or NMDA receptor dysfunction
NMDA antagonist (PCP, ketamine)
GABAergic Interneuron
5-HT2A agonist (LSD, psilocybin)
Excess serotonin or 5-HT2A receptor upregulation
Pyramidal Neuron
Visual hallucinations
Ventral Striatum
Hallucinations and delusions
Excess dopamine, D2 receptor upregulation, or dopaminergic agents
Raphe
Ventral Tegmental Area (VTA)
D2 antagonist (antipsychotic)
D2 agonism* (cocaine, amphetamine)
*DAT antagonism leading to more available dopamine
5-HT2A receptor
NMDA receptor
D2 receptor
α2 GABA receptor
Serotonin
Glutamate
Dopamine
GABA
Inhibitory signal
Stimulatory signal
Hyperactive
Induces psychosis
Blocks psychosis


Pimavanserin
5-HT2A antagonist/inverse agonist
(and to a lesser extent 5-HT2C)
Direct Effect
Serotonin
Mitigates the effects of excessive serotonin signaling via 5-HT2A receptors (potentially due to too little GABA signaling)
Dopamine
Reduces hyperactive signaling in the mesolimbic pathway resulting in less stimulation of D2 receptors in the ventral striatum
Glutamate
Reduces hyperactive signaling to the VTA resulting in less stimulation of the mesolimbic pathway

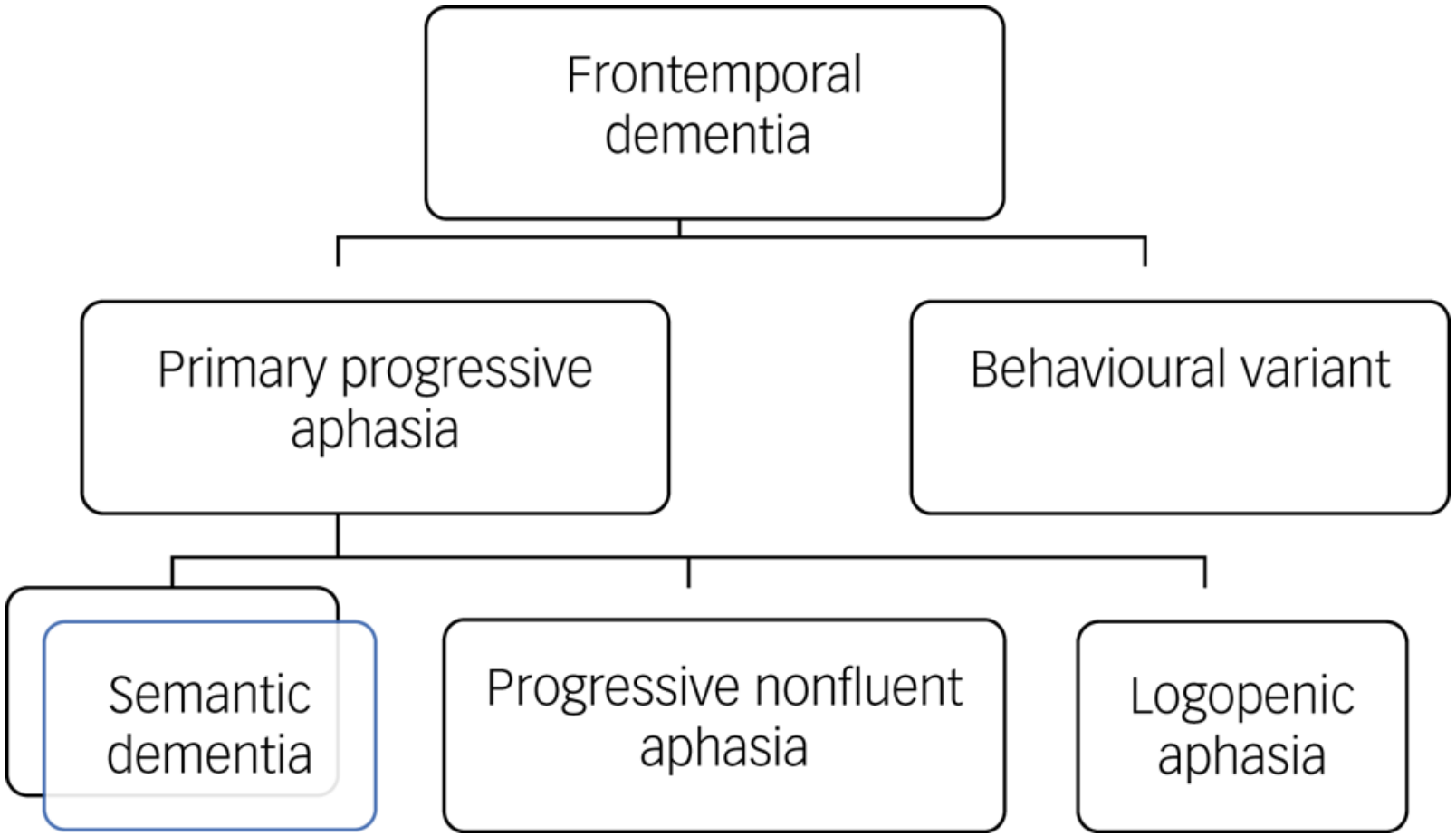
FTD

- FTD is a complex disease, accounting for 13% of all cases of young-onset dementia (people<65 years old) and comprising approximately 3% of all dementia cases.
- It affects frontal lobes, anterior temporal obes, or both, with reduced performances on behavioural control, emotion regulation and language .
- The estimated incidence of FTD is 2.7–4.1 per 100,000 people
- FTD prevalence is 15–22 per 100,000.
- Between 30 and 50% of patients report a family history of the disease.
- Mutations in two genes, microtubule associated protein tau (MAPT) and progranulin (GRN) account for about half of these cases,


Frontotemporal dementia
Sporadic
Genetic
Tau
TDP-43
FUS
Tau
TDP-43
FUS
Other
CBD
PSP
Pick's
GGT
A
B
C
aFTLDU
Other
MAPT
C9orf72
GRN
TBKI
Other
FUS
CHMP2B

- Particularly, familial FTD due to the C9ORF72 mutation is linked with psychiatric disturbance, with up to 50% of patients exhibiting delusions or hallucinations
- Identifying bvFTD is also challenging because symptoms features traditionally fall within the realm of psychiatry.
- One study showed that as many as 21% of autopsy-verified FTD

patients were misdiagnosed with psychosis or SCH


Frontemporal dementia
Primary progressive aphasia
Behavioural variant
Semantic dementia
Progressive nonfluent aphasia
Logopenic aphasia

- The major clinical differences between SCH and FTD are about onset and progression.
- FTD typically begins in people above 45 years of age whereas in SCH the onset is below such a period.
- FTD progresses constantly towards a severe decline while the course is different for patients with SCH .
- FTD evolves into profound dementia and even death whereas the likelihood that patients with SCH show clinical worsening appears to be correlated with the duration and number of positive symptoms. They could also reach a relatively stable plateau.

- Patients with young onset FTD may be diagnosed with psychotic illness years before the diagnosis of dementia.
- An approximate prevalence of psychotic symptoms in FTD is equal to 10%.
- In particular, hallucinations have been described in patients with ubiquitin-positive and transactive response DNA-binding protein-43 (TDP-43)-positive pathologies (FTLD-U-TDP) and with progranulin gene mutations.
- Among patients with C9ORF72 mutation, a relatively high proportion have late-onset positive symptoms

Negative Symptoms in bv-FTD

- Blunting
- loss of empathy
- complete lack of emotional display
- showing little warmth and often seeming indifferent to the feelings of the others.
- Particularly, the association between negative symptoms and impaired medial prefrontal functions in bvFTD could support the hypothesis that they may be framed within the frontal lobe syndrome, as primarily hypothesized for negative symptoms in patients with SCH.

- . Schizophrenic patients show deficits across a large number of neurocognitive domains such as
- speed of processing,
- attention,
- working memory, verbal/visual learning and memory,
- reasoning,
- problem solving
- verbal comprehension .
- It is unclear if patients with SCH stable cognitive dysfunction versus progressive or late .cognitive decline

- Social cognition as the ability of processing social stimuli—is a rapidly emerging area of study in SCH.
- Patients often display marked impairments in such a cognitive and motional skill resulting in misinterpretations of social intent of other persons, withdrawal and impaired daily interpersonal functioning
- It is unclear whether the impairment is present at the beginning and if the degree of the impairment progressively increases or decreases
- Studies have provided empirical support for social cognitive deficits in bvFTD, as well, including impaired ability to process facial emotions, detect socially inappropriate speech, adopt perspective of another person, solve social dilemmas, and perceive sarcasm or react to fearful or sad stimuli

- An interesting research perspective [38] suggested that while
- current deficits in social and interpersonal functioning in
- patients with FTD may reflect a decrement in previously
- acquired skills, similar deficits in patients with SCH may
- reflect an overall inadequately learned process.

- Cognitive dysfunction, although usually overshadowed by prominent behavioural disturbances, is still an important feature in bvFTD.
- Impairment of executive functions including planning, judgement, problem-solving and mental flexibility is characteristic of FTD, whereas memory, visual perception, and spatial skills are relatively preserved.

- Differentiating between SCH and FTD represents a serious clinical problem with respect to diagnosis and treatment.
- neuropsychological assessment that seems promising in differentiating between these two conditions by detecting specific patterns of neurocognitive deficits as well as
- neuroimaging.
- Follow-up visits are also required to better discriminate between SCH and FTD.
- Genetic counselling and testing are useful in individuals with family history of frontotemporal degeneration, as well

- Typically, misidentification delusions and delusions of a persecutory nature such as paranoid, jealousy or partition delusions are reported in late onset psychosis .
- Partition delusions encompass the belief that people, substances, objects or radiation can pass through what would normally be a barrier.
- Visual and auditory hallucinations are also frequently observed (

- Even though a slightly differing presentation of psychotic symptoms may already prove useful in differential diagnosis, an overlap in the phenomenology of psychosis in different diseases is still important, creating the need for further investigation

- Some authors suggest a lateralized effect, as they have noticed associations between left lateralized abnormalities and persecutory
- delusions as opposed to right lateralized abnormalities and misidentification delusions. Others have observed more pronounced cognitive impairment in individuals who experience misidentification as opposed to persecutory delusion

- misidentification might result from further deterioration of the occipital and/or parietal cortices—the primary visual cortex or visual association areas—combined with frontal abnormalities.
- Visual (or auditory) hallucinations appear to co-occur with misidentification delusions in some cases, and they are also assumed to arise in part as a result of (right) parietal or (medial) temporal abnormalities—which suggests the involvement of the dorsal and
- ventral visual pathways—combined with frontal dysfunction

- mechanism underlying the occurrence of hallucinations is hypothesized to be inefficient suppression of (personal) memory recall and reality monitoring, suggesting an interplay between executive and memory function coinciding with a frontotemporal neurobiological set of deficiencies .
- In line with the hypothesis of impaired memory functioning in hallucinations, some authors have described memory impairment in delusions.
- They speculate that delusions might be linked conceptually to memory deficits because a failure to recall accurate information enables the development of inaccurate beliefs in order to explain the current reality

- Still, the importance of additive impairments, specifically concerning executive functioning, cannot be underestimated as this prevents the individual from changing his mind leading to a “delusionally” stern conviction rather than a confabulation which can be corrected.

- Indeed, a comparison of imaging results in patients with AD with and without paranoid beliefs showed more reduced metabolism in the:
- right superior dorsolateral frontal cortex
- the right inferior frontal pole
- the right lateral orbitofrontal cortex as well as a decreased brain volume in orbitofrontal and medial frontal areas in individuals with paranoid belief

- we expected a certain degree of overlap in the cognitive profile of individuals with late onset psychosis transdiagnostically, as a result of a common underlying set of neurobiological alterations related to the development of psychosis.
- However, we also hypothesized that there were disease-specific differences in the profiles that are irrelevant to the development of psychotic symptom.

- Research focussing on AD versus DLB shows that in AD there is predominantly memory and language dysfunction which is associated with temporal atrophy and/or hypometabolism in the early stages of the disease leading to impairments in semantic networks.
- DLB, on the other hand, is initially characterized by executive dysfunction, reduced processing speed, impaired (visual) attention and visuospatial perceptual/constructive deficits.

- Although sometimes quantitative measures of neuropsychological task performance are comparable, there may be qualitative differences. For instance, memory function is characterized by retrieval problems in DLB, whereas both encoding/storage
- and retrieval are affected in AD (Ballard et al., 1999; Cagnin et al., 2015; Ferman et al., 2006; Goldmann Gross, Siderowf, &
- Hurtig, 2008; Oda, Yamamoto, & Maeda, 2009; Walker, Allen, Shergill, & Katona, 1997; Yoon, Kim, Moon, Yong, &
- Hong, 2015). Coincidently, a measure of recognition shows more rapid decline in AD than in DLB at follow-up (Stavitsky
- et al., 2006). Visuoconstructive deficits are also different in nature in patients with AD and DLB. Even though both groups
- are equally impaired in drawing from memory, the patients with DLB are usually more impaired in copying (MetzlerBaddeley, 2007). Such a pattern confirms that a primary memory/semantic problem interferes with visuoconstructive abilities
- in AD, whereas a perceptual problem interferes with visuo-construction in DLB

Visuoconstructive deficites

- equally impaired in drawing from memory
- the patients with DLB are usually more impaired in copying
- Such a pattern confirms that a primary memory/semantic problem interferes with visuoconstructive abilities in AD, whereas a perceptual problem interferes with visuo-construction in DLB.

- object recognition skills appear similar in both conditions but an analysis of the nature of mistakes in a naming task showed
- that patients with AD displayed more semantic paraphasias, whereas individuals with DLB showed more visuoperceptual mistakes when asked to recognize and name an object
- Psychomotor slowing is comparable in both disorders, though its origin differs
- Specifically, patients with AD show impairment in perceptuomotor and decision processes leading to psychomotor slowing, whereas patients with DLB exhibit visual and attention deficits that contribute to psychomotor slowing

- .
- In addition, patients with DLB exhibit more severely reduced letter fluency than individuals with AD
- we expected patients with VLOSLP and AD+P to perform similarly on language tests, whereas individuals with DLB were expected to do better.
- Finally, patients with DLB were likely to perform slightly worse on tasks involving perceptual abilities such as visuospatial perception or visuo-construction compared to both other conditions.

Cognitive impairment in AD DLB VLOSP

- Impaired attention

- Impaired EF
- Impaired processing speed

More AD than DLB or VLOSP

- Impaired learning
- Impaired consolidation
- Impaired language
- Nearly intact visuconstruction

More DLB than AD or VLOSP

- Impaired visuoconstruction
- Better memory
- Better language