INVESTIGATING NEUROPATHOLOGICAL CORRELATES OF HYPERACTIVE AND PSYCHOTIC SYMPTOMS IN DEMENTIA, A SYSTEMATIC REVIEW

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INTRO

Neuropsychiatric symptoms frequently complicate the phases of cognitive worsening of dementia. They are defined as: behavioral-psychological symptoms of dementia or **BPSD**. In this spectrum, **the HIDA-P cluster is difficult to manage and severely impacts caregiving**. Pathophysiology and neuropathology underlying HIDA-P remain poorly understood.

AIMS

To clarify what is known about the **neuropathology of the HIDA-P cluster**, to elucidate wether different **protheinopathies** are associated with peculiar symptoms and which are the **neural circuits associated with these symptoms**

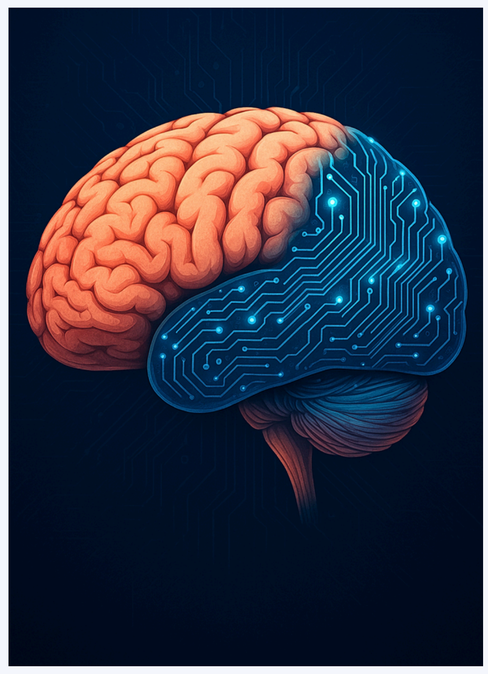
HOW?

PRISMA guidelines, with a systematic search across MEDLINE, CENTRAL, and EMBASE databases.

37 OUT OF 846 ARTICLES MET INCLUSION CRITERIA FOR A TOTAL OF 18823 CASES:

Clinical Diagnosis	% of cohort	HIDA-P symptom	Prevalence %
Alzheimer's disease	83%	Agitation / aggression	14
Frontotemporal dementia	13%	Delusions	11,6
Dementia with Lewy bodies	5%	Disinhibition	7,61
—	—	Hallucinations	6,83
—	—	Irritability	7
—	—	Aberrant motor	5,4

Lesion / pathology	Agitation / Aggression	Disinhibition	Delusions	Hallucinations
Tau (ADNC, Braak III-VI)	**+++**	**+++**	**+++**	**+++**
α-Synuclein (Lewy bodies)	++	+	++	++
TDP-43 (LATE-NC)	++	+	+	+
Mixed (Tau + α-syn ± TDP-43)	**++++**	**++++**	**++++**	**++++**
Vascular / CAA	– / ±	–	±	±



TAKE HOME MESSAGE

- **TOPOGRAPHY WINS OVER CHEMISTRY – LESION LOCATION AND BURDEN, NOT SPECIFIC PROTEINOPATHIES, DICTATE HIDA-P BEHAVIOURS.**
- **AMYGDALA-CENTRIC LIMBIC DYSFUNCTION - TAUOPATHY AND COMBINED PROTEINOPATHIES INTO THE AMYGDALA AND THE LIMBIC SYSTEM REPRESENT THE MORE FREQUENT NEUROPATHOLOGY RELATED TO THE HIDA-P CLUSTER**
- **MIXED PROTEINOPATHIES (TAU + A-SYNUCLEIN ± TDP-43) AMPLIFY SYMPTOM SEVERITY – MULTITARGET THERAPIES REQUIRED.**
- **NO BEHAVIOUR IS PATHOGNOMONIC – HALLUCINATIONS, DISINHIBITION AND AGGRESSION OCCUR ACROSS ALZHEIMER, FTD, DLB AND MIXED CASES.**

SOME REFLECTIONS

- ➤ **SHIFT FROM PROTEIN-NAMED DIAGNOSES TO CIRCUIT-BASED STAGING THAT MAPS LIMBIC-FRONTAL NETWORK DAMAGE.**
- ➤ **DEPLOY LIMBIC-TARGETED TAU-PET AND EMERGING A-SYNUCLEIN PET AS RISK-STRATIFIERS AND TRIAL BIOMARKERS.**
- ➤ **TEST COMBINATION DISEASE-MODIFYING STRATEGIES (ANTI-TAU + ANTI-SYN) TO CURB DISRUPTIVE BEHAVIOURS.**
- ➤ **USE HIGH-RESOLUTION DIGITAL PHENOTYPING (WEARABLES, IN-HOME SENSORS) TO REFINE CLINICOPATHOLOGICAL CORRELATIONS.**
- ➤ **EXPAND COHORTS TO VASCULAR DEMENTIA, UNDER-REPRESENTED ETHNICITIES AND PRODROMAL (MBI) STAGES FOR TRUE GENERALISABILITY.**
- ➤ **INTEGRATE NEURO-IMMUNE INDICES (MICROGLIAL ACTIVATION, ASTROCYTIC REACTIVITY) WITH PROTEINOPATHY STAGING TO UNCOVER NEW TARGETS.**

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