INPLASY

INPLASY2024100082

doi: 10.37766/inplasy2024.10.0082

Received: 1 October 2024

Published: 1 October 2024

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Investigating Neuropathological Correlates of Hyperactive and Psychotic Symptoms in Dementia: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - This open-access publication is provided by the SERPERO Foundation (20129, Milan, Italy), and tge Golgi Cenci Foundation (20081, Abbiategrasso, Italy) in equal parts.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024100082

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 October 2024 and was last updated on 18 October 2024.

INTRODUCTION

Review question / Objective This systematic review aims to summarize the current evidence regarding the neuropathological basis underlying the HIDA and psychosis (HIDA-P) domains of BPSD. Specifically, it seeks to elucidate whether distinct proteinopathies are associated with various individual symptoms within the HIDA-P domains. Furthermore, the review investigates whether these proteinopathies spread according to specific patterns throughout the brain, affecting distinct neural circuits depending on the symptoms.

Condition being studied According to the current definition, major Neuro-Cognitive Disorder (NCD), which corresponds to dementia, is a clinical syndrome characterised by a significant cognitive decline in one or more cognitive domains interfering with the independence of activities of daily living. In addition to cognitive impairment, neuropsychiatric symptoms, also referred to as Behavioural and Psychological Symptoms of Dementia (BPSD), are highly prevalent and significantly complicate the clinical course of dementia. BPSD can be found in almost all types of dementia, each of which has distinct characteristics depending on the specific form. At a certain stage in the clinical course, over 80% of individuals with cognitive impairment will exhibit BPSD, which contribute significantly to the cost of dementia care. Various studies have categorised these symptoms into distinct clusters. Among these, Van Der Linde et al conducted a systematic analysis of 62 studies utilising unbiased clustering approaches. This analysis identified the following BPSD domains: the affective domain, the psychosis domain (including hallucinations and delusions), the apathy domain, and the euphoria and hyperactivity-impulsivity-irritability-disinhibition-aggression-agitation (HIDA) domain. Notably, the psychosis and HIDA domains, which have a prevalence rate of 17% to 40%, pose

considerable challenges in the management of dementia patients. The BPSD underlying neuropathological correlates remain largely unexplored. Given that certain BPSD are integral to the core diagnostic criteria of various NCDs, their neuropathological basis may depend on the specific proteinopathy involved (i.e. visual hallucinations caused by Lewy Type Synucleinopathy - LTS - in patients with DLB) or on the dysfunction of particular underlying neural circuits (e.g., limbic system dysfunction leading to disinhibition in patients with Fronto-Temporal Lobar Degeneration - FTLD). Alongside pure neurodegenerative diseases, mixed pathologies are frequently identified, which involve the same neuronal circuits and complicate the accurate definition of the underlying basis of BPSD due to the numerous possible combinations of proteinopathies. Therefore, what is the role of combined pathologies and their topographical distribution in this context? Further, due to the limited number of studies, some of which present contradictory findings, it is challenging to conduct a comprehensive analysis of the available data concerning the neuropathology of BPSD. This is particularly true for the psychosis and HIDA domains, which have unfavourable prognostic implications and impose a significant burden on caregivers, thereby representing the greatest therapeutic challenge.

METHODS

Participant or population The inclusion criteria involved studies whose aim is to examine neuropathologically the HIDA cluster and/or psychosis domain in human subjects with dementia. Studies attributing BPSD to an underlying psychiatric diagnosis were excluded from the analysis.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Searches were limited to human studies and English language articles without any date restriction. Conference papers, posters, abstracts, letters to the author, editorials, and reviews were excluded.

Eligibility criteria The inclusion criteria involved studies whose aim is to examine neuropathologically the HIDA cluster and/or psychosis domain in human subjects with dementia. Studies attributing BPSD to an underlying psychiatric diagnosis were excluded from the analysis.

Information sources The PICO portal (automation tool software version 3.0.2023.1205) was used to screen the imported records.
Studies were identified by a systematic search of the MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases.

Main outcome(s) Not applicable.

Quality assessment / Risk of bias analysis The included studies' quality assessment was assessed using the Newcastle–Ottawa Scale (NOS) (26) and the CARE Guidelines.

Strategy of data synthesis A narrative synthesis of data extracted from the eligible records was carried out to summarise the information. The relevant measures were extracted, harmonised, and summarised into descriptive statistics, including the number (n), mean, and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. General descriptive statistics were presented as weighted means and weighted standard deviations (SDW). A meta-analysis could not be performed due to the considerable heterogeneity in the data reported across the included studies, which prevented the identification of uniform variables necessary for inferential statistical analysis.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Country(ies) involved Italy.

Keywords neuropathology, BPSD, neuropsychiatric symptoms, psychosis, dementia, Alzheimer, Lewy Bodies, FTLD.

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