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COMMENTARY

Relationship between neuropsychiatric symptoms, cognition, and neuroimaging in mild cognitive impairment: Are we there yet?

Commentary on "Neuropsychiatric symptoms and their neural correlates in individuals with mild cognitive impairment" by De Lucia *et al.*

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Neuropsychiatric symptoms (NPSs) in mild cognitive impairment (MCI), an intermediate state between normal aging and dementia, are gaining much attention. Prevalence rates of at least one NPSs range from 35% to 85% in MCI patients, with hospital-based samples reporting a higher global mean prevalence of any NPS than population-based studies (60% vs. 45%, respectively) (Martin and Velayudhan, 2020; Monastero *et al.*, 2009). Most studies have focused on the prevalence of NPSs in MCI and their association with risk of conversion to dementia (Martin and Velayudhan, 2020). Studies have also investigated NPSs for their associations with either cognitive or neuroimaging markers in MCI. Depression, one of the most common NPS of MCI, was associated with reduced cortical thickness in the entorhinal cortex at baseline and accelerated atrophy in anterior cingulate cortex (Zahodne *et al.*, 2013). Brain average controllability of the default mode network of MCI patients with depression ($n = 15$) was shown significantly decreased compared to cognitively normal subjects ($n = 15$) and MCI patients without depression ($n = 30$) (Fang *et al.*, 2021). The authors found further attenuated controllability in the left superior prefrontal cortex of these patients, relative to the MCI patients without depression, explaining the loss of ability for depressed patients to respond to cognitive control tasks, such as controlling emotion or setting and planning goals (Fang *et al.*, 2021). MCI patients with apathy performed worse in global cognition and executive function tests compared to patients without apathy, particularly in decision-making tasks (Bayard *et al.*, 2014; Connors *et al.*, 2023). Apathy in MCI has been associated with executive function deterioration and deficits in posterior cingulate and with cortical thinning in inferior temporal and anterior cingulate cortices (Mortby *et al.*, 2022; Velayudhan, 2023). Anxiety in MCI has been associated with impairments in global cognition and episodic and verbal memory, as well as executive dysfunction (Beaudreau and O'Hara, 2008). Agitation has been associated with greater memory impairments and deficits in visuospatial abilities in MCI individuals (Brodaty *et al.*, 2012). Evidence suggests that nighttime disturbance and excessive daytime sleepiness are associated with slower reaction times and impairments in attention and memory, and thus, interfere with cognitive performance of MCI patients in neuropsychological tests (Martin and Ancoli-Israel, 2008). Appetite/eating abnormalities have been associated with worse performance in language, learning and memory, and euphoria in episodic memory in 222 patients with MCI (Lü *et al.*, 2021). In a study where the the neuropsychiatric Inventory-Questionnaire (NPI-Q) items were loaded into four factors (elation, psychosis, depression, and motor behavior), the NPS factor elation, consisting of the NPI-Q items euphoria and disinhibition, had a significant positive association to the thickness of the right anterior cingulate cortex across groups including MCI ($n = 102$) (Siafarikas *et al.*, 2021). The anterior cingulate cortex conceptualized as an executive region of the brain was also found as an anatomic region also for agitation and delusions in 72 people with cognitive impairment including MCI ($n = 27$) (Nowrangi *et al.*, 2021). Most of these studies were cross-sectional, included patients of MCI along with other groups such as dementia and used magnetic resonance imaging for neuroimaging markers and

Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) as the cognitive measure.

A recent paper in *International Psychogeriatrics by* De Lucia *et al.* (2023) is novel and interesting in that they looked at associations of NPSs with cognitive dysfunctions and their neuroanatomical correlates. More specifically, they sought to characterize the association of global NPSs burden with grey matter volume and tau deposition in predefined brain regions. They obtained data for 233 MCI patients and 305 healthy adults for comparisons from third study phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI-3) database (please see adni.loni.usc.edu for more information) from September 2021 to December 2021. All the participants had undergone a comprehensive neuropsychological assessment to assess all cognitive domains, volumetric MR brain scan, and Tau positron emission tomography scans with Flortaucupir (AV-1451) for in vivo assessment of regional tau deposition. De Lucia *et al.* (2023) selected regions of interest based on previous studies and included middle frontal region, orbito-frontal region, amygdala, hippocampus, anterior cingulate cortex, posterior cingulate cortex, striatum, and the composite regions Braak 3–4 and Braak 5–6. They divided MCI participants into those without NPSs (MCI^-) ($n = 90$) and those with at least one type of NPS (MCI^+) ($n = 143$). De Lucia *et al.* (2023) reported 61.4% MCI subjects had at least one NPS, with the most prevalent ones being depression (26.1%), irritability (23.6%), and sleep disturbances (23.6%). Their major finding was that the global burden of NPSs in MCI was associated with regional brain atrophy and with impairment in frontal/executive function, but not with regional tau deposition. More specifically they found that MCI^+ participants showed significantly poorer performance on MMSE, Alzheimer 's disease Assessment Scale-Cognition (ADAS-Cog) (Rosen *et al.*, 1984) memory subsets, ADAS-cog naming and trial making (part B and B–A) compared to MCI^- individuals. Secondly, De Lucia *et al.* (2023) demonstrated that MCI subjects with NPSs showed reduced brain volumes in the orbitofrontal and posterior cingulate cortices and further showed that among the regional volumetric measures, posterior cingulate cortex volume was the only predictor for the total NPI scores in this population. Finally, they did not find any significant difference in tau deposition between the two groups in all the predefined brain regions. The tau deposition too did not predict the total NPS scores. De Lucia *et al.* (2023) also analysed the most frequent behavioral symptoms in this cohort (i.e., depression, irritability, sleep disturbances, apathy, and agiation) with orbitofrontal cortex and bilateral posterior cingulate cortex, but did not find significant associations.

De Lucia *et al.* (2023) study expands not only on the prevalence of NPSs in MCI which are in keeping with other studies (Lü *et al.*, 2021) but also their associations with cognitive dysfunctions and brain regional volumes. They also establish a lack of association between NPSs with tau deposition as seen by others (Sun *et al.*, 2021). De Lucia *et al.* (2023) used comprehensive cognitive assessments beyond the MMSE. However, the study was limited to cross-sectional analysis. They also did not compare individual NPSs with regional brain volumes or the tau deposition, but restricted it to the total neupsychiatric scores. Future studies incorporating comprehensive neuropsychological testing of specific cognitive domains affected longitudinally by specific NPS and their associations with neuroimaging markers would help to examine the pathways of disease progression and potential targets for treatment response.

With the growing availability of biomarkers and better classifications, NPS is also being compared for MCI distinguished as MCI with Lewy bodies (MCI-LB) with those with MCI due to Alzheimer's disease (MCI-AD), and MCI-LB are seen to have higher total NPS with more prevalence for core features such as visual hallucinations and rapid eye movement sleep behavior disorder or REM behavior disorder (Liu *et al.*, 2021). It is important for future studies to distinguish the subtypes and their associations with cognition and neuroimaging markers, for better underdstanding of underlying neuropathologies, and to help precision medicion with target population for appropriate pharmacological and nonpharmacological interventions in people with MCI.

Conflict of interest

None.

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