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Conceptual clarity and valid measurement are needed to improve research on depression in dementia

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Costello, Roiser, and Howard (2023) examine the nature, mechanisms and treatment of depression in dementia in their timely review. While outlining important avenues potentially leading to better pharmacological treatment of depression in dementia, the authors also show the conceptual challenges inherent in studying neuropsychiatric symptoms in dementia, of which depression is a prime example. In this brief commentary, I wish to expand on the authors' examination of the clinical construct we know as depression in dementia by including both the broader perspective of depression assessment and the results of recent studies in dementia specifically.

Depression in dementia can be considered distinct compared to major depressive disorder in the cognitively unimpaired (Olin, Katz, Meyers, Schneider, & Lebowitz, 2002), but there are at least three conceptual and methodological similarities between the two fields. The first is the challenge of valid and reliable measurement of depression (Fried, Flake, & Robinaugh, 2022). Commonly used measures of depression in dementia can be roughly divided into three groups: those used in screening and diagnosis of depression with no special focus on dementia or ageing, those with a focus on geriatric psychiatry and those specifically designed for dementia. While using dementia-specific rating scales appears to be the best option, the validity evidence for even the most commonly used instruments is relatively scarce (e.g. Perrault, Oremus, Demers, Vida, & Wolfson, 2000). This lack of evidence calls into question how well we are assessing depression (and not agitation, sleep disturbances, apathy, anxiety, cognitive symptoms, etc.), an observation also raised by the authors. Moreover, many of the earlier neuropsychiatric symptom measures derive their validity evidence from samples that had more severe dementia than individuals coming to memory clinics today.

Aiming for operational criteria of depression is another point of convergence between dementia and the general population. There are numerous diagnostic and research criteria for neuropsychiatric syndromes in dementia, including depression (Olin et al., 2002). The Diagnostic and Statistical Manual for Mental Disorders (DSM; American Psychiatric Association, 1994) has been considered an example to strive for, and existing criteria for psychiatric disorders have been used as a starting point for neuropsychiatric syndrome criteria in dementia (Saari, 2023). Relatively absent, however, is the critical discussion of diagnostic criteria in neuropsychiatric syndromes (including depression) in light of the substantive criticism levelled at diagnostic criteria of psychiatric syndromes (e.g. Andreasen, 2007; Frances & Widiger, 2012; Haslam, McGrath, Viechtbauer, & Kuppens, 2020). The critical discussion in neuropsychiatric syndromes of dementia has largely focused on incremental changes in existing criteria to accommodate research advances rather than more fundamental aspects of the process, such as how transparently the criteria are formulated and how possible concerns from the scientific community or the general public are handled (Frances & Widiger, 2012; Saari, 2023).

Owing to the pathological and clinical heterogeneity in dementia, it appears that there is no *a priori* reason to assume that the diagnostic and research criteria of neuropsychiatric syndromes are working significantly better than they are in psychiatry. For depression specifically, there are data indicating that the National Institute of Mental Health-Depression in Alzheimer's disease (NIMH-dAD) criteria (Olin et al., 2002) identify more individuals as depressed compared to the DSM-IV criteria (American Psychiatric Association, 1994) in line with the requirement of less symptoms and a shorter persistence than the DSM criteria (Sepehry et al., 2017). However, Sepehry et al. (2017) concluded that the reliability of the NIMH-dAD criteria still needs to be established. Furthermore, a certain circularity cannot be avoided in comparing the diagnostic properties of the NIMH-dAD to the DSM criteria of major or minor depressive disorder that served as the foundation for the NIMH-dAD criteria.

The third area of overlap, which relates to the preceding observations, is the debate on the nature of depression as continuous or categorical. As yet, there appears to be no conceptual consensus on whether depression in dementia is a distinct categorical entity (present or not), or

continuous in the same sense as cognitive symptoms. Based on extensive empirical research, most diagnostic constructs in psychiatry, including mood disorder, tend to be better represented as continuous dimensions (Haslam et al., 2020). It seems at least plausible that depression in dementia could be continuous in nature owing to progressive neurodegeneration and various psychosocial factors. If depression in dementia was continuous, it would benefit clinical trials as continuous outcomes provide an increase in statistical power (Markon, Chmielewski, & Miller, 2011).

A possibly fruitful way forward, as also suggested by the authors, is to step outside the traditional thinking in diagnostic categories and sum-scores by examining how depressive symptoms connect to another as networks. The authors propose viewing depression as 'a complex system of interacting depressive symptoms, which differs across dementia subtypes and stages of disease' (Costello et al., 2023). There are some studies that, taken together, may elucidate the dynamics of depressive symptoms from normal cognitive ageing to dementia.

A network analytic study found that the symptoms of lack of happiness and worthlessness were among the most central depressive symptoms in cognitively unimpaired older adults, and that apathy and depressive symptoms were highly interwoven (van Wanrooij, Borsboom, Moll van Charante, Richard, & van Gool, 2019). In our own study, we found a highly similar network structure to that of van Wanrooij et al. in patients with (mostly very mild or mild) AD, with helplessness and lack of happiness again as the most interconnected symptoms, with worthlessness also emerging as one of the more central features (Saari, Hallikainen, Hintsa, & Koivisto, 2020). The network structure was also highly similar after 1 year of follow-up. An earlier study by Masters, Morris, and Roe (2015) found that individual depressive symptoms did not appreciably differ between individuals who remained cognitively unimpaired and those with cognitive decline in follow-up. The only depression symptom that predicted cognitive decline was, unsurprisingly, 'having more memory problems than most' (as was also found in van Wanrooij et al. 2019).

Taken together, the three studies show tentative evidence that there are no marked qualitative changes in the dynamics of individual depressive symptoms between normal cognitive ageing and mild AD; evidence to the contrary in AD may partly be explained by the use of total scores of depression rating instruments. However, some caveats should be kept in mind. First, the participants in these studies did not need to meet criteria for depression and different network structures might emerge in clinically depressed individuals without cognitive impairment compared to those with dementia. Next, the authors (Costello et al., 2023) cite two studies in Parkinson's disease, where depression symptom profiles differed between depressed older adults with and without Parkinson's disease and individuals with Parkinson's disease with and without dementia, respectively (Ehrt, Brønnick, Leentjens, Larsen, & Aarsland, 2006; Riedel, Heuser, Klotsche, Dodel, & Wittchen, 2010). It appears that different neurodegenerative diseases may result in different depressive symptom profiles and larger deviations from depressive symptom profiles in those without cognitive impairment. Finally, there is a need to examine the effects of antidepressant treatment on the network structure of depression (Costello et al., 2023).

In addition to similarities in conceptualising and assessing depression in dementia and depression in those without cognitive impairment, a key difference is that in dementia, depression is often assessed by an informant. This difference was also noted by the authors, but the implications may deserve further comment as depressive symptom ratings from different raters tend to produce discrepant results in cognitively normal ageing (Georgi, Vlckova, Lukavsky, Kopecek, & Bares, 2019) and in individuals with dementia (O'Sullivan et al., 2022; Saari et al., 2020). It is acknowledged that caregiver burden (Pfeifer et al., 2013), anosognosia (Verhülsdonk, Quack, Höft, Lange-Asschenfeldt, & Supprian, 2013) and the various neurocognitive changes outlined by the authors (Costello et al., 2023) may drive discrepancies between self-ratings and informant-ratings. In addition to these clinical and psychosocial factors of the disease, there may also be more fundamental psychometric and psychological factors at play. For instance, informant-ratings tend to understandably emphasise explicit signs and symptoms of depression which may only represent a part of the depressive symptoms experienced by the patient (Mograbi & Morris, 2014). There is also a basic asymmetry in how people view themselves *v.* how they view others (Pronin, 2008), which may explain why a perfect convergence between rating modalities is unachievable even under the most optimal conditions. Rather than trying to decide which rating modality is the least biased, other fields have attempted to create methods for integrating ratings of multiple modalities, which, in testing, have provided better predictive utility than any single rating (Makol et al., 2020).

In sum, there appears to be much for dementia research to still learn from the trials and errors in conceptualisation and assessment of depression in the cognitively healthy population. It is hoped that research aiming to refine the concept(s) and measurement of depression in dementia would be met with more enthusiasm and urgency. With future treatment studies in mind, more attention should be paid to defining what depression in dementia is and is not and how to best assess depression at various stages of cognitive decline.

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