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COMMENTARY

Objective *versus* subjective indicators of neurocognitive status

Subjective memory complaints (SMCs) are one of the potential diagnostic criteria for major and mild neurocognitive disorder (NCD) listed in the *Diagnostics & Statistics Manual, 5th Edition* (American Psychiatric Association, 2013). However, the diagnostic utility of self-reported SMCs remains uncertain given inconsistent and, at times, contradictory findings in the extant literature. Accumulating evidence suggests SMCs may be more closely related to one's psychological or emotional status (e.g. mood symptoms, perceived stress) than their objective memory functioning (Desai *et al.*, 2021; Yates *et al.*, 2017). Such findings highlight the importance of identifying valid and reliable markers of memory dysfunction that are objectively measured and less susceptible to reporting bias or distortion. While neuropsychological testing might be considered the gold standard in this regard, test performance can also be affected by the psychological and emotional context in which an evaluation is completed, such as one's preexisting expectations or concerns about their memory ability. Thus, diagnostic precision could be further enhanced by identifying neural markers that serve as reliable proxies for memory function irrespective of other individual or situational factors.

In their paper entitled, "Subjective, Neuropsychological, and Neural Markers of Memory in Older Adults," Sheffler *et al.* (2021) investigated one such neural marker: the P300 event-related potential (ERP) component. In a sample of 79 community-dwelling older adults, they examined the associations between P300 amplitude (derived from a visual go/no-go oddball paradigm), objective verbal memory performance on a widely used list learning task, SMCs, NCD diagnostic severity ratings (i.e. possible/probable normal, mild, or major NCD), and several psychosocial variables (i.e. perceived stress, psychological well-being, anxiety, and depression). After adjusting for relevant demographics, they observed that P300 amplitude was significantly associated with long-delay recall and diagnostic ratings, whereas SMCs were only associated with anxiety, depression, perceived distress, and worse psychological well-being.

This well-designed study is a valuable contribution to the field with several notable strengths. First and perhaps most importantly, this paper adds to the growing body of research that suggests self-reported SMCs in older adults may be sensitive indicators of current mood and distress, but not of objective memory status. From a clinical translation perspective, this finding reinforces the importance of gathering information from multiple informants as part of the NCD evaluation process, while at the same time suggesting SMCs may be a marker of underlying affective rather than memory disorder in older adults, though these are not mutually exclusive.

Another noteworthy strength of this study is the multimodal approach to examining the complex relationship between P300 amplitude, memory recall, SMCs, NCD diagnostic ratings, and psychological/emotional well-being. These are all important factors to consider as part of a comprehensive NCD assessment, and investigating them concurrently in a within-subjects design provides a robust empirical foundation from which to interpret and extend their findings. In this vein, the association between P300 amplitude and both delayed recall and NCD diagnostic rating lends support to previous research suggesting lower P300 amplitude could be a candidate neural marker of cognitive impairment in Alzheimer's disease (Hedges *et al.*, 2016). More broadly, the author's decision to focus on P300 amplitude is significant given how extensively this ERP component has been studied at multiple levels of analyses (Polich, 2007) and across a range of neuropsychiatric populations (Patrick *et al.*, 2015; Shahaf, 2019). This knowledge base will be invaluable in future efforts aimed at applying these and related experimental findings to clinical practice. Toward that end, one of this study's co-authors (GH) has previously identified three potential clinical uses of ERPs more broadly: predictors of risk, predictors of treatment change, and targets for change (Hajcak *et al.*, 2019). However, considerable research is still required before ERP waveform analysis can be used in routine clinical practice. Regarding the P300 specifically, further investigation is needed to establish a more nuanced understanding of how the P3a and P3b subcomponents relate to objective memory metrics, with the latter appearing to relate more to subsequent memory processing (Polich, 2007). Moreover, at a practical level, the

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cost of ERP procedures in terms of equipment, time, and personnel may be prohibitive for many providers outside of specialized memory clinics. Nevertheless, the potential clinical applications of ERP are intriguing, especially if used in concert with other behavioral and biological measures within a precision medicine framework.

Third, Sheffler *et al.* discuss several relevant limitations of their study that should serve as guideposts for future research. Chief among these is the lack of diversity within their sample – a problem that is not unique to this study. On the contrary, this remains a pervasive problem within Alzheimer's research that limits the generalizability of findings and compounds existing disparities in healthcare access and outcomes (Babulal *et al.*, 2019). Given that Sheffler *et al.*'s findings were derived from mostly White and highly educated individuals, future studies will benefit from a more inclusive and concerted focus on other demographic factors, such as race/ethnicity and socioeconomic status, which may play critical roles in the association between SMCs and objective memory or diagnostic ratings. For example, recent population-based research has found that Black and Hispanic older adults are more likely to rate their memory positively despite having measurable impairment, whereas White older adults are more likely to rate their memory abilities negatively in the absence of objective impairment (Jang *et al.*, 2022). This differential pattern could reflect underlying factors, such as health literacy and cultural beliefs, though the exact reasons remain unclear. This is a consequential gap in knowledge, and it is therefore imperative that future studies seeking to extend Sheffler *et al.* do so through a more culturally inclusive lens.

Of note, several articles published in a recent volume of *International Psychogeriatrics* demonstrate that more inclusive research efforts are underway. For example, Nielsen and Jørgensen (2020) examined the diagnostic accuracy and utility of a brief screening assessment (Rowland Universal Assessment Scale) as an education-unbiased dementia screener that is easily transferable across cultures. In addition, a study by Teresi *et al.* (2020) focused on measurement invariance of stress assessment among Hispanic dementia caregivers. Sample limitations notwithstanding, Sheffler *et al.*'s P300 findings can also potentially inform more culturally sensitive diagnostic practices given that previous research has suggested the P300 may be robust to education or cultural effects (Campanella, 2013).

When assessing for potential NCDs in older adults, the diagnostic utility of self-reported cognitive decline, including SMCs, remains an open question. While empirical evidence increasingly suggests that SMCs are likely, at least in part, a reflection of one's psychological and emotional well-being, findings are less consistent regarding their association with objective measures of cognitive impairment. Previous findings have been limited by a paucity of sample diversity – a limitation that recent research suggests could have a meaningful impact on the cultural generalizability of prior studies (Jang *et al.*, 2022). Thus, efforts to identify biomarkers that are reliably associated with cognitive/memory function *and* are culturally unbiased should be a research priority in the field. The paper by Sheffler *et al.* focuses on one candidate neural marker that has the potential to address this need: the P300 ERP waveform. While further investigation is needed before the P300 can be used routinely in clinical practice, this study represents a promising step in that direction.

Conflict of interest

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Description of authors' roles

Both authors contributed equally to literature review and manuscript preparation.

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