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Subjective, neuropsychological, and neural markers of memory in older adults

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ABSTRACT

Objectives: To investigate the relationship between the P300 event-related potential, neuropsychological measures of memory, subjective memory complaints (SMCs), and indicators of psychosocial functioning.

Design, setting, and participants: In this cross-sectional study of 79 community-based older adults, aged 60–75 years, participants completed online surveys and in-person neuropsychological and electroencephalogram (EEG) assessments.

Measurements: Measures included: the Change subscale of the *Metamemory in Adulthood Questionnaire*, NIH Toolbox Emotions battery (Perceived Stress and Psychological Well-Being), *Geriatric Depression Scale*, *Geriatric Anxiety Scale*, electrocortical measures (EEG), *California Verbal Learning Test*, 3rd Edition, and diagnostic ratings for mild and major neurocognitive disorders based on full neuropsychological battery, clinical interview, and two-clinician consensus.

Results: P300 amplitude was associated with long-delay verbal memory recall and diagnostic rating. SMCs were not associated with objective memory or diagnostic rating. SMCs were associated with higher perceived stress, anxiety, and depression symptoms and lower psychological well-being.

Conclusions: Neural indicators such as the P300 may be useful for early detection of cognitive impairment. SMCs were not a reliable indicator of early memory impairment in relation to neuropsychological or neural indicators, but may be a useful indicator of unreported stress and mood symptoms in clinical settings.

Key words: P300 ERP, subjective memory complaints, cognitive functioning

Objective

Understanding early indicators of dementia may be key to improving quality of life and treatment for the millions of older adults affected by dementia each year (Alzheimer's Association, 2013). Subjective memory complaints (SMCs) are a component of subjective cognitive decline, defined as a "self-perceived decline in any cognitive domain over time (Jessen *et al.*, 2014)." SMCs have been identified as a potential early marker of Alzheimer's disease (AD) pathology that may be informative prior to detectable changes in objective performance. In fact, SMCs are frequently used in research and clinical work as a sole proxy assessment of cognitive impairment in older adults. However, this practice may be problematic given that current guidelines indicate that SMCs should never be sufficient to diagnose even preclinical AD (Jessen *et al.*, 2014). Further, diagnosis of Mild and Major neurocognitive disorder (NCD) requires both subjective and objective evidence of decline (American Psychiatric Association, 2013). The current study examines the utility of SMCs in relation to objective cognitive impairment and NCD diagnosis.

The evidence for a relationship between SMCs and objective cognitive impairment is mixed and often contradictory (Crumley, *et al.*, 2014; Lenehan, *et al.*, 2012; Reid and MacLullich, 2006; Roberts, *et al.*, 2009; Mitchell *et al.*, 2014 ; Weber and Maki, 2016). However, SMCs *are* consistently associated with depression and anxiety symptoms in both cognitively normal and cognitively impaired older adults (Yates, *et al.*, 2017; Norman *et al.*, 2020 ;

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Song *et al.*, 2020). For example, Yates *et al.* (2017) found that SMCs were more strongly related to mood problems than objective impairment, both cross-sectionally and longitudinally. Meta-analyses demonstrate that SMCs and objective memory are correlated, but the effect is small and influenced by psychosocial factors, including depression and anxiety (Crumley, *et al.*, 2014). Other researchers, however, have found that SMCs may be useful *predictors* of cognitive decline in individuals who are cognitively intact (Tsutsumimoto *et al.*, 2017). These seemingly contradictory findings may be due to examining SMCs in patients at specific stages of impairment; thus, we examined individuals with a range of impairment from cognitively normal to objective and diagnosable impairment.

In addition to subjective assessments of memory function, biological markers are needed to improve diagnostic accuracy in relation to NCDs and risk. Neural measures assessed using electroencephalogram (EEG), such as the P300 component of the event-related potential (ERP), may serve as an early indicator of memory impairment related to Mild and Major NCDs (Howe, *et al.*, 2014; Waninger *et al.*, 2018). The use of ERPs to examine cognitive impairment in older adults is a growing area of study. The P300 component is associated with genetic risk for AD (Howe, *et al.*, 2014), objective measures of MCI (Waninger *et al.*, 2018), and cognitive decline more broadly (Polich, 2004). Thus, ERPs hold the potential to be a low-cost biomarker for early cognitive decline that can be administered and interpreted on-site and therefore, may serve as a tool for detecting the earliest stages of dementia (Newsome *et al.*, 2013).

Our study builds on prior literature using a multimodal approach to assess the utility and reliability of SMCs in relation to P300 amplitude, objective measures of memory, and NCD diagnosis in a sample of primarily healthy older adults. Specifically, we expected that 1) P300 amplitude would be associated with other objective measures of memory performance and NCD diagnosis, 2) based on a majority of studies reviewed, SMCs would not be associated with objective memory performance, P300 amplitude, or NCD diagnosis, and 3) SMCs *would* be related to higher levels of stress, depression, and anxiety symptoms, and lower levels of overall psychological well-being.

Methods

Participants and procedures

Participants included 79 community-dwelling older adults (aged 60–75) recruited from the [Blinded for Review] with e-mails including a link to complete an online recruitment survey. Participants (N = 517) completed an initial online survey that assessed for SMCs, along with a range of other health and psychosocial information. One hundred and twenty individuals were e-mailed with the goal of identifying 80 participants who met inclusion criteria. Participants with self-reported family history of AD and worse self-reported memory were prioritized for initial contact in order to increase the likelihood of identifying participants with mild NCD. Eighty five of these 120 participants responded with interest in the study. Of the 85, 79 participants completed at least one of the two, in-person appointments. The first appointment included review of the informed consent form, a clinical interview, and a battery of neuropsychological assessments (reported below), which lasted approximately 2.5 hours. At the second appointment, participants completed the emotions battery of the NIH Toolbox and an EEG to assess the P300. The second visit lasted approximately 1.5 hours. This study was approved by the [Blinded for Review], and written informed consent was provided from all participants.

Self-report measures

Subjective memory complaints

SMCs were measured by the Change subscale of the Metamemory in Adulthood questionnaire (McDonough *et al.*, 2020), which consists of 10 items assessing age-related memory changes over the past 10 years (e.g., "The older I get the harder is it to remember clearly" and "Compared to 10 years ago, I am much worse at remembering titles of books, films, or plays."). This subscale was chosen based on prior work demonstrating good reliability and validity in relation to memory performance (McDonough *et al.*, 2020). Table 1 provides a list of all items included in the measure. Participants rated the degree to which they agreed with each statement on a scale from 1 (agree strongly) to 5 (disagree strongly). Items were recoded, such that a higher score corresponded with more SMCs (range = 10–45; Cronbach's alpha = 0.88).

Perceived stress

Perceived stress was measured using the NIH Toolbox Emotion Battery (Kupst *et al.*, 2015). Participants rated 10 items (e.g., "How often have you felt nervous and "stressed"?) based on their experience over the past month on a scale from 1 (never) to 5 (very often).

Psychological well-being

Psychological well-being was measured using the NIH Toolbox Emotion Battery, which includes

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Table 1. Metamemory in adulthood questionnaire change subscale items

1.	My memory for names has declined greatly in the last 10 years.
2.	The older I get the harder it is to remember clearly.
3.	My memory for dates has declined greatly in the last 10 years.
4.	I am less efficient at remembering now than I used to be.
5.	I am just as good at remembering as I ever was.
6.	Compared to 10 years ago, I am worse at remembering titles of books, films, or plays.
7.	I misplace things more frequently now than when I was younger.
8.	I am much worse now at remembering the contents of news articles and broadcasts than I was 10 years ago.
9.	I can remember things as well as always.
10.	Compared to 10 years ago I now forget many more appointments.

the following subscales: positive affect, general life satisfaction, and meaning and purpose (Gershon *et al.*, 2013). Uncorrected T-scores, which compare performance to the entire NIH toolbox nationally representative adult sample, were used in analyses.

Depression

Depression was measured with the Geriatric Depression Scale (GDS; Yesavage and Sheikh, 1986), which includes 15 yes/no questions (e.g., "Do you feel that your life is empty?") based on how participants felt over the past week. Items are summed, resulting in a possible score from 0 to 15. A total score was also calculated after excluding item 10 (i.e., "do you have more problems with memory than most"), which was also included and reported in the analysis and results.

Anxiety

Anxiety was measured with the Geriatric Anxiety Scale (GAS; Segal *et al.*, 2010), which includes 10 symptoms of anxiety or stress (e.g., "I could not control my worry.") that are rated over the past week from 0 (not at all) to 3 (all of the time).

EEG recording and P300 Task

Tasks used to elicit the P300 component are important to consider when studying an older adult population. For example, hearing impairments are often used as exclusion criteria for auditory ERP tasks, which may exclude many older adult participants, given that up to 80% of older adults may have some level of hearing loss (Sprinzl and Riechelmann, 2010). Thus, visual ERP tasks eliciting the P300, which may be more sensitive for detecting cognitive changes (Waninger *et al.*, 2018), were used for the current study.

Continuous EEG was recorded with an active 32-electrode system (ActiCHamp, Brain Products, GmBH; Munich, Germany) while participants completed a visual go/nogo computer task during which they were presented a stream of continuous stimuli and asked to use a mouse click to blast aliens (frequent targets, 70%) and asteroids (infrequent targets, 15%), but not astronauts (non-targets, 15%). The task consisted of 10 blocks of 40 trials each. Each trial consisted of the stimulus presented for 200ms, followed by a blank screen for 1000 ms and then a fixation cross presented for 300–700 ms (in 100 ms intervals).

Data processing

EEG data were processed using Brain Vision Analyzer, Version 2.1 (Brain Products, Gilching, Germany). Data were re-referenced to the average of the mastoid electrodes and filtered from 0.1 to 30 Hz (Butterworth, 4th order). Stimulus-locked epochs were created with a duration of 1450 ms, beginning 200 ms prior to stimulus onset, and corrected for eye movement artifacts using the algorithm developed by Gratton *et al.* (1983). Segments that contained voltage steps >50 μV between sample points, a voltage difference of 175 μV within a 400 ms interval, or a maximum voltage difference of <0.5 μV within 100 ms intervals were automatically rejected. Data were further segmented by trial type (i.e., alien, asteroid, astronaut), with epochs spanning 1200 ms beginning 200 ms prior to stimulus onset. Baseline correction was then applied using the 200 ms pre-stimulus interval and stimulus-locked ERPs were averaged for each trial type separately. Parietal P300 amplitude was scored as the mean area at Pz between 350 ms and 600 ms following the presentation of frequent and infrequent targets (asteroids and aliens, respectively). Two participants were excluded from ERP analyses due to either poor EEG quality or insufficient task accuracy. A P300 difference score was then created by subtracting frequent targets (i.e., aliens) from infrequent targets (i.e., asteroids) to isolate the P300 (i.e., oddball) response to the infrequent targets versus frequent targets; this difference score was used in all subsequent analyses.

Neuropsychological performance and diagnostic rating

Objective memory performance

Objective memory performance was measured with the California Verbal Learning Test, 3rd Edition

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Table 2. Neuropsychological diagnosis rating

DIAGNOSTIC RATING	CRITERIA	FREQUENCY IN SAMPLE
1. Probable normal	No subjective or objective evidence of impairment **AND** all scores are within the normal range for age and level of education	42
2. Possible normal	Limited evidence of either subjective (e.g., greater effort in ADLs, more reliance on lists etc.) **OR** limited objective evidence of decline that is not in the impaired range (e.g., low average) that is not consistent with level of education	15
3. Possible mild NCD	Evidence of either subjective decline in memory and greater use of compensatory strategies **OR** poorer performance than expected in one or more cognitive domain **OR** limited evidence of impairment in both subjective and objective findings	12
4. Probable mild NCD	Evidence of subjective decline in memory and/or greater reliance on compensatory strategies for ADLs **AND** poorer performance than expected in one or more cognitive domain (e.g., borderline or impaired range)	7
5. Possible major NCD	Evidence of *significan*t subjective decline in memory that interferes with ADLs and greater use of compensatory strategies **OR** significant objective impairment in one or more cognitive domain (e.g., severely impaired range)	2
6. Probable major NCD	Evidence of significant subjective decline in memory that interferes with ADLs **AND** significantly poorer performance than expected in one or more cognitive domain	1

Diagnostic ratings (1–6) were based on consensus between two independent raters after a clinical interview and brief neuropsychological battery completed with the participant. ADL = activities of daily living.

(CVLT-3; Delis *et al.*, 2017), which is a well-validated measure of short and long-delay verbal recall. Scaled scores (normed by age group) were used in analyses.

Diagnostic rating

Participants completed a brief clinical interview and a short neuropsychological battery, including the following tests: The Test of Premorbid Functioning, the Brief Visuospatial Memory Test-Revised, the Wechsler Memory Scale 4th edition Logical Memory subtest, the CVLT-3, subtests from the Wechsler Adult Intelligence Scale-IV (i.e., Digit span, Block design, Similarities), a clock drawing, FAS and Animal Naming, Delis-Kaplan Executive Function System Trails subtests, the Boston Naming Test, the GDS, and the GAS. Based on the pattern of standardized scores (standardized based on age and education when possible) and information obtained during the clinical interview, participants were assigned a diagnostic rating based on review by two clinicians—one licensed clinical psychologist and a psychology resident. Ratings ranged from 0 to 6 (1 = probable normal, 2 = possible normal, 3 = possible Mild NCD, 4 = probable Mild NCD, 5 = possible Major NCD, 6 = probable Major NCD), with higher indicating a greater level of impairment. Ratings were based on DSM-5 diagnostic criteria for Mild and Major NCD, including information from a clinical interview and neuropsychological battery developed by a board certified geropsychologist. If there was limited evidence of either subjective *or* objective impairment, a "possible" rating was given consistent with the level of impairment. For example, a rating of "possible Mild NCD" was established if a participant denied subjective decline or use of compensatory strategies, but performed below expectations on multiple objective tests of memory, whereas, a "probable Mild NCD" was based directly on DSM-5 criteria for a Mild NCD. See Table 2 for full diagnostic rating criteria.

Analysis

All statistical analyses were conducted using IBM SPSS Statistics 26. Linear regression models were used to assess the relationships between SMCs, psychosocial variables, and objective measures of cognitive functioning while controlling for age, gender, and education. Unstandardized slope estimates are reported for all regressions. Age was not controlled for in analyses predicting standardized neuropsychological outcomes (i.e., CVLT-3), as these were already normed based on age group.

Results

The final sample was comprised of 79 older adults (63.3% female) aged 61–75 years ($M = 68.10$, $SD = 3.88$). Most participants identified as White (77.2%; 11.4% Black; 3.8% Asian; 7.6% other) and had a college degree or higher (79.7%). Seven participants were excluded from EEG analyses due to incomplete or unreliable data. Approximately

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Table 3. Means, standard deviations, and correlations

VARIABLE	*M*	*SD*	1	2	3	4	5	6	7
1. Subjective memory complaints	28.89	7.05	–						
2. Perceived stress	44.07	8.67	0.36**	–					
3. Psychological well-being	52.32	8.06	−0.23***	−0.55**	–				
4. Depressive symptoms	1.33	1.91	0.42**	0.43**	−0.55**	–			
5. Anxiety symptoms	3.58	2.45	0.44**	0.54**	−0.44**	0.46**	–		
6. Verbal memory short delay	12.02	3.43	0.02	−0.05	0.16	−0.12	−0.01	–	
7. Verbal memory long delay	11.76	3.7	0.01	−0.01	0.14	−0.1	−0.01	0.80**	–
8. P300 amplitude (μV)[a]	11.31	4.54	0.04	0.01	0.26*	−0.16	−0.15	0.24***	0.38**

[a]P300 outliers removed ($n = 4$).
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.056$.

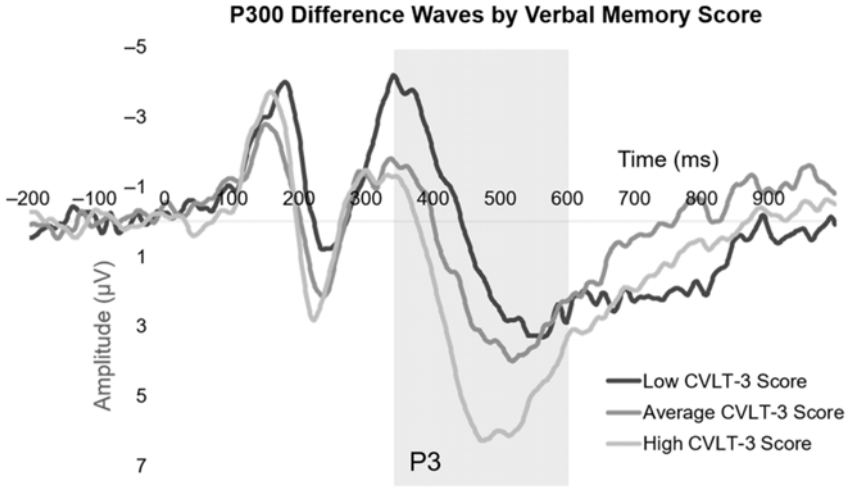

Figure 1. Grand averaged difference waveforms (infrequent targets–frequent targets) for participants who scored below average ($n = 11$), within the average range ($n = 19$), and above average ($n = 39$) on a neuropsychological assessment of verbal memory (i.e., CVLT-3 long delay). Average range was indicated by a scaled score of 8–12.

24.1% of the sample met diagnostic criteria for possible or probable Mild NCD; however, the majority of participants scored in the average or above range on an objective verbal memory task (i.e., CVLT long delay: 83.5%). See Table 3 for descriptive statistics and bivariate correlations.

Controlling for gender and education, we assessed whether our objective measures of memory (i.e., CVLT-3 recall scores) were associated with the P300. Increased P300 amplitude was associated with higher long-delay verbal memory recall score ($b = 0.43$, $t(65) = 2.84$, $p = .006$, partial $r^2 = 0.11$; see Figure 1), although the relationship was non-significant with the short-delay verbal memory recall score on the CVLT-3 ($b = 0.28$, $t(65) = 1.90$, $p = 0.062$). Further, lower P300 amplitude was significantly associated with higher (i.e., worse) diagnostic rating ($b = -0.11$, $t(64) = -2.23$, $p = 0.029$, partial $r^2 = 0.07$; see Figure 2), controlling for age, gender, and education.

Consistent with our prediction on the relationship between SMCs and objective cognitive measures, results of multiple regression analyses controlling for gender and education level revealed that SMCs were not associated with short-delay ($b = -0.018$, $t(72) = -0.32$, $p = 0.747$) or long-delay verbal memory recall scores on the CVLT-3 ($b = -0.05$, $t(72) = -0.79$, $p = 0.432$). Further, controlling for age, gender, and education level, SMCs were also not associated with diagnostic rating ($b = 0.026$, $t(71) = 1.29$, $p = 0.198$) or P300 amplitude ($b = 0.036$, $t(61) = 0.71$, $p = 0.481$).

Finally, results of multiple regression analyses controlling for age, gender, and education level indicated that SMCs *were* associated with higher perceived stress ($b = 0.43$, $t(65) = 3.07$, $p = 0.003$, partial $r^2 = 0.13$), depression ($b = 0.12$, $t(69) = 4.47$, $p < 0.001$, partial $r^2 = 0.23$), and anxiety symptoms ($b = 0.15$, $t(71) = 3.88$, $p < 0.001$, partial $r^2 = 0.17$). The relationship between SMCs and depression

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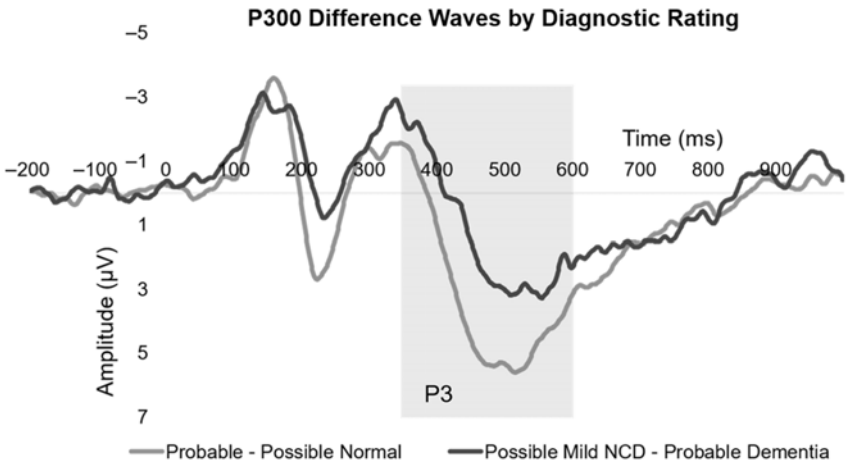

Figure 2. Grand averaged difference waveforms (infrequent targets – frequent targets) for participants with probable – possible normal diagnostic ratings ($n = 52$) and possible Mild NCD – probable dementia diagnostic ratings ($n = 17$).

remains significant ($b = 0.10$, $t(69) = 3.87$, $p < 0.001$, partial $r^2 = 0.18$), even if item 10 (i.e., "do you have more problems with memory than most") is removed from the total score. SMCs were also associated with worse overall psychological well-being ($b = -0.29$, $t(65) = -2.09$, $p = 0.040$, partial $r^2 = 0.06$).

Conclusions

Subjective reports of cognitive decline, including SMCs, are currently a component of the diagnostic criteria for DSM-5 Mild and Major NCD diagnoses —and yet the literature is not clear as to whether these complaints actually relate to objective cognitive impairment. The current study took a multimodal approach to examine objective measures of cognitive functioning, including neuropsychological test performance, diagnostic ratings, and neurophysiological measure of cognitive functioning (i.e., the P300). Critically, all of these objective measures related to one another—findings which bolster construct validity. However, none of these measures related to subjective complaints, which were only associated with psychosocial indicators of distress.

In the current study, SMCs were related to mood and psychosocial difficulties rather than objective measures of neural and cognitive functioning. Specifically, SMCs were related to higher levels of perceived stress, more depressive and anxiety symptoms, and worse overall psychological well-being. Our findings are consistent with prior literature demonstrating that SMCs are strongly influenced by mood and may not be a reliable indicator of cognitive impairment or progression to dementia (Balash *et al.*, 2013; Brodaty *et al.*, 2017; Edmonds *et al.*, 2014). These results add to a literature questioning the utility of SMCs as a criterion in the diagnosis of Mild or Major NCDs. However, there is a growing literature demonstrating that psychiatric symptoms such as depression and anxiety may have predictive utility as markers of neurodegenerative disease (Liew, 2019; Liew, 2020). Further, research suggests that SMCs may be most valuable as a disease indicator prior to the onset of objective impairments (Jessen *et al.*, 2014). Thus, in future research, it may be important to examine whether the predictive validity of SMCs and mood symptoms may be strongest prior to the onset of objective impairments, while reported SMCs may decline as NCDs progress and insight also declines.

NIH has indicated the importance of identifying neuromarkers of DSM-5 diagnoses such as Mild and Major NCDs. In this regard, our findings provide support for further examination of P300 amplitude as a neuromarker for detecting early memory impairments in aging. Specifically, we found that P300 amplitude was associated with participants' current diagnostic rating, and with a key clinical measure of amnestic-type memory impairment that has been most closely linked to AD (Newsome *et al.*, 2013). Prior research has also demonstrated that ApoE €4 carriers, individuals at increased risk for AD, are characterized by reduced P300 amplitude (Irimajiri, *et al.*, 2010; Lai *et al.*, 2010). Further, prior research suggests that ERPs may provide a measure of cognitive functioning that is not influenced by cultural or education effects (Campanella, 2013). These advantages, combined with our findings, support the potential use of P300 amplitude obtained from visual tasks as an important neural indicator of cognitive impairment—consistent with NIH's vision of identifying neurocorrelates of

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neuropsychiatric disorders. However, given the relatively small effects detected in the current study, additional research is needed.

Limitations and future directions

Though demographics within the current sample are consistent with the geographical area from which they reside, the higher levels of education and socioeconomic status may limit generalizability. Although the sample included mostly healthy older adults, a number of participants met criteria for possible Mild NCD or greater impairment. Although this sample is appropriate for identifying early cognitive changes in relatively healthy older adults, the current sample could not assess these relationships among individuals with more marked impairment—which will be an important avenue for future research. Additionally, the current study emphasized objective verbal memory, which may not generalize to non-Alzheimer's types of Major NCDs (e.g., fronto-temporal, vascular, etc.). Finally, recent research indicates that age-anchored measures of SMCs comparing performance to an individual's peers may be most reliably related to objective cognitive impairment (Chapman *et al.*, 2021; Perrotin *et al.*, 2012; Tandetnik *et al.*, 2015). The measure used in the current study was anchored based on intra-individual change, which supports prior work demonstrating that these types of memory complaints in particular may be unrelated to objective functioning.

Future research may benefit from examining the generalizability of these findings to more diverse populations and individuals with clinically diagnosed NCDs. Further, the use of additional neuropsychological tests that allow for differential diagnosis of Mild and Major NCD subtypes may improve the specificity and application of these results to clinical settings. Finally, examination of these relationships longitudinally will be vital in determining the predictive utility of both P300 amplitude and SMCs. Future studies might examine the degree to which the P300 may provide an early indicator of impairment, and whether it prospectively predicts decline. Further, studies examining SMCs should include both age-anchored and intra-individual measures.

Summary and recommendations

Many individuals develop concerns about their thinking and memory as they age, which may lead to selective attention to memory problems and increased SMCs. This may be especially common among individuals who are experiencing high stress, anxiety, and depressive symptoms. Our study adds to the previous literature by demonstrating that SMCs were most strongly associated with recent stress, overall psychological well-being, depression, and anxiety symptoms—and were unrelated to objective memory impairment associated with NCDs. Further, the P300 was associated with objective, but not subjective impairment, demonstrating the potential utility for this measure for early detection methods. However, future research is needed to evaluate the sensitivity of the P300 amplitude across more diverse, severe, and under-represented populations.

It is important to acknowledge that memory complaints obtained from a significant other still provide significant diagnostic value, as these are less influenced by a patient's mood or stress. Thus, when a patient reports SMCs, collecting additional information from a significant other may be key to determine an accurate diagnosis (as is suggested in the DSM-5). When a significant other is not available, SMCs should be queried with specific questions to determine a patient's use of compensatory strategies that are a change from previous functioning. Such descriptions may allow clinicians to determine if a referral for objective testing may be beneficial, but retain the potential to be diagnostically misleading. For example, it is common for individuals with both Mild NCD and AD to lack insight into their impairment and deny memory problems entirely (Mak *et al.*, 2015).

Despite the disadvantages of SMCs in relation to cognition, SMCs may provide valuable clinical information about the patient's subjective experiences and potential psychological and psychosocial concerns that should be assessed. For example, SMCs may provide a pathway for healthcare workers to identify a need to assess for otherwise unreported mood and anxiety problems among older patients. This is important because older adults may not necessarily associate their cognitive complaints with stress, anxiety, or depression, and therefore, they may not seek appropriate treatment. Further, our results do not preclude the potential usefulness of SMCs as a potential risk indicator in the pre-prodromal phase of NCDs before objective impairment arises. Finally, our results support the recommendation by previous studies to re-evaluate patient reported SMCs as a diagnostic criterion for Mild NCD (Lenehan, *et al.*, 2012) and provide support for further examination of P300 amplitude as an additional, less biased assessment. Ultimately, research consistently supports that objective testing for cognitive impairment provides the most consistent and sensitive measure of early cognitive changes, and the P300 may be a useful addition in research and clinical practice.

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Conflict of interest

The authors report no conflicts with any product mentioned or concept discussed in this paper.

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Description of authors' roles

J. Sheffler, M. Meynadasy, and G. Hajcak, study completion, conceptualization, and composition of total article and analysis. D. Taylor and D. Kiosses, writing and editing. All authors reviewed the final version and agree to be accountable for all aspects of the work.

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