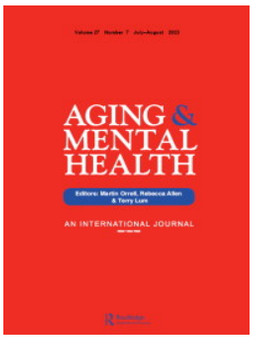

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Influence of affective states on informant impression of neuropsychiatric symptoms in people living with MCI

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ABSTRACT

Objectives: Alzheimer's disease (AD) and mild cognitive impairment (MCI) are often accompanied by neuropsychiatric symptoms (NPS; e.g. depression/apathy/irritability) causing challenges for people living with dementia/caregivers and predicting worse disease progression. Accurately assessing NPS is critical to research on AD/MCI. However, there are limitations to both self-reports and clinician evaluations; the field often relies on informants to assess NPS. Informants' perception of NPS are influenced by disease and caregiver factors that may lead to biased assessments. We aimed to assess the relationship between participants self-reported affective states (valence/arousal) and informant-reported NPS.

Methods: Data from a double-blinded intervention design (primarily testing neurostimulation's effect on NPS) were used to examine the relationship between participant-reported affective states and informant-reported NPS over 1 month. Forty participants (24 females) with MCI and NPS (mean age = 71.7, SD = 7) were enrolled along with informants (primarily spouses/partners) who regularly interact with participants. NPS assessment occurred weekly and at pre- and post-intervention, and participant-reported affective states were assessed at 14 timepoints.

Results: Generalized Estimating Equations showed that participant levels of arousal, but not valence, were significantly related to corresponding informant-reported NPS at weekly (arousal: $B = -0.59$, SE = 0.27, Wald's $\chi^2 = 4.61$, $p = .032$; valence: $B = 0.17$, SE = 0.19, Wald's $\chi^2 = 0.80$, $p = .37$) and pre-/post- (arousal: $B = -4.00$, SE = 1.58, Wald's $\chi^2 = 6.42$, $p = .011$; valence: $B = -3.34$, SE = 1.80, Wald's $\chi^2 = 3.43$, $p = .06$) assessments.

Conclusion: The findings indicate that informant-reported NPS may be more strongly influenced by arousal, and informants may be less attuned to valence in people living with MCI.

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Introduction

Alzheimer's disease (AD) is widely known as a disease affecting cognition in older adults; however, AD is often accompanied by a variety of behavioral symptoms known as neuropsychiatric symptoms (NPS). Individuals living with dementia may begin to experience NPS at different points in the disease progression; however, population-based studies have shown that about 50% of people living with mild cognitive impairment (MCI; a clinical precursor to AD) experience at least one NPS (Cummings, 2020). The prevalence of NPS in MCI highlights the importance of NPS as a treatment target early in disease progression. In the earlier stages of cognitive decline, individuals with MCI commonly experience NPS including depression, apathy, and anxiety (García-Martín et al., 2022). As cognition deteriorates further, severe NPS, such as delusions, hallucinations, and/or aggression, increase in prevalence (García-Martín et al., 2022; Lyketsos et al., 2011), and become a major source of distress for both people living with dementia and their caregivers (Ballard et al., 2008).

Developing treatments that target NPS in people living with MCI and AD requires accurate assessments of NPS. However, clinicians and researchers face challenges in accurately assessing NPS in their patients/participants. Self-report measures are subjective, and with worsening cognition and NPS, there is the risk that individuals' self-reported symptoms and severity become less reliable (Cosentino & Stern, 2005; Rosen et al., 2014) (e.g. anosognosia has been widely reported among people living with dementia (Lin et al., 2010; Rahman-Filipiak et al., 2018; Starkstein et al., 2006)). Clinicians' observational assessments of NPS are the gold standard, but it is usually only possible to conduct assessments occasionally (e.g. once every 6 months/year; Gitlin et al. (2014)), and this may not fully capture the dynamics or fluctuations of NPS. The field therefore largely relies on informants (i.e. individuals, including caregiving, who have regular interactions with the people living with dementia) to assess NPS. However, previous studies suggest that informants tend to over- or underestimate individuals' NPS (Stella et al., 2015) compared to clinician evaluations. Informants may also perceive the quality of life of a person living with MCI as much worse, based on their NPS, than the individuals' experiences themselves (Conde-Sala et al., 2009). Caregiver burden increases with worsening NPS symptoms (Terum et al., 2017), and can also influence how informants rate the individuals' NPS and cognitive status (Persson et al., 2015). Overreliance on informant reports may, therefore, undermine accurate evaluation of the effects that NPS have on a person living with MCI's daily living activities and quality of life (Votruba et al., 2015).

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There is a need to fully elucidate the potential biases in informant ratings of NPS to better inform research and assessment.

Emotion and affect change moment-to-moment based on a person's internal state (Rottenberg, 2005). Affect is thought to consist of two dimensions—arousal (i.e. the level of activation or excitement one experiences, ranging from calm/peaceful to excited/agitated) and valence (i.e. the level of pleasantness one experiences, ranging from negative to positive). While recent research suggests that these two dimensions of affect may not be fully independent or fundamental (Yik et al., 2022), they represent dissociable dimensions that are useful in understanding older adults' affective states: in samples in the US, ratings of valence and arousal have been shown to share ~11% of variance (Yik et al., 2022), showing that they capture distinct information about affective state. Emerging work suggests these affective states commonly seen in normal emotion literature can be used to evaluate abnormal emotion, including aspects of emotional dysregulation that manifest as NPS. For example, some recent studies linked arousal (Shinohara et al., 2020) and valence (Medeiros et al., 2020) to severity of depression. Similar linkages have been found between arousal or valence and other NPS such as anxiety or apathy (Eling et al., 2006; Xu et al., 2018). Additionally, it has been suggested that informants may base their ratings of symptoms, like depression, on visible signs of the individual's affect (Saari et al., 2020). This has important implications for research on NPS, as this research suggests that informants may rely more heavily on different aspects of affect when rating NPS, leading to the over- or under-reporting of certain symptoms. Hypothetically, informants may rely disproportionately on behavior that overtly indicates affective state, especially when a person living with MCI has difficulty communicating more subtle aspects of their internal state.

In the present article, we aimed to understand how participant-reported ratings of valence and arousal related to how informants rate NPS in individuals living with MCI. We used data from an intervention study (primarily designed to test the effects of brain stimulation on NPS; described in Clinical trial.gov NCT04099524) to examine the proposed relationship between informants' assessment of NPS in individuals living with MCI and those individuals' affective state over a 4-week period. The use of data from an intervention design allows us to model co-fluctuations in affective state and NPS over a 4-week period, providing a more precise understanding of the dynamic relationships than would be possible in a cross-sectional study. Specifically, we were interested in understanding whether arousal and valence might be differentially associated with informant ratings of NPS, with important implications for research on NPS that relies on informant reports.

Methods

Study design

The data from this study was part of a larger double-blinded randomized controlled trial, primarily aimed at understanding the effect of brain stimulation on NPS (Turnbull et al., 2023). The intervention lasted for one month, where an intervention versus active control protocol was provided for 14 sessions. We collected informants' rating of NPS in individuals living with MCI at pre- and post-intervention using the neuropsychiatric inventory (NPI) and weekly (throughout the intervention) using the Neuropsychiatric Inventory-Questionnaire (NPI-Q). During the 14 intervention sessions, the participant affective state was assessed before the intervention began (see Figure 1).

Participants

We enrolled 40 community-dwelling participants (24 females and 16 males) with MCI and NPS-Q ≥ 3 at baseline from local clinics: mean age 71.7 (SD = 7.0), average 16 years of education (SD = 2.7), mean global cognition score via Montreal Cognitive Assessment at 23.33 (SD = 2.57). Inclusion criteria included (1) consensus diagnosis of MCI due to Alzheimer's disease (AD) based on 2011 NIA-AA diagnostic criteria (Montreal Cognitive Assessment version 2 education-adjusted total score of $18 \leq x \leq 26$; one standard deviation below age- and/or education-corrected population norms for Rey's Auditory Verbal Learning Test (Lists C&D); preserved activities of daily living via self-report version of the Activities of Daily Living-Prevention Instrument total score ≤ 30; and absence of dementia); (2) presence of two neuropsychiatric symptoms with informant-rated Neuropsychiatric Inventory Questionnaire (NPI-Q) severity sum score ≥3, rated by comparing to 6 months ago to capture a worsening trajectory; (3) stable memory medications for at least 3 months and stable anti-depressant, anti-psychotic, or anti-anxiolytic medication for at least one week prior to screening; and (4) adequate visual and hearing acuity for testing. Participants with MRI (e.g. pacemaker) or tDCS (e.g. history of seizures,

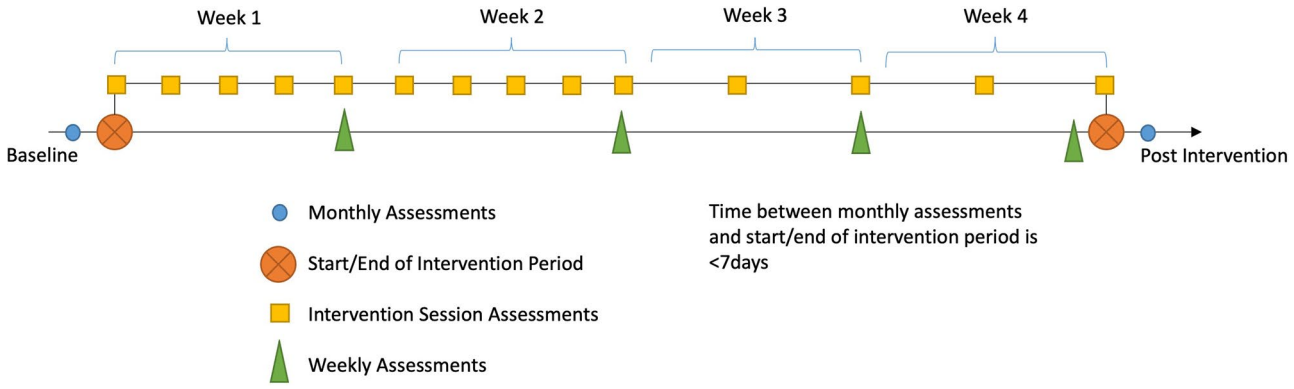

Figure 1. Study design. Participants took part in intervention sessions in a 5-5-2-2 format over the 4- week period. Prior to each assessment they completed the Self-Assessment Manikin (SAM) to provide levels of valence and arousal. Informants completed the Neuropsychiatric Inventory (NPI) at pre- and post-intervention assessments, and were contacted once per week during the 4-week intervention period to complete the Neuropsychiatric Inventory-Questionnaire (NPI-Q). Models were created using corresponding SAM/NPI (-Q) values: pre- and post-intervention NPI assessments were matched with the first and last SAM assessment (intervention session), and weekly NPI-Q assessments were matched with the last SAM assessment (intervention session) for each week. SAM assessments and weekly NPI-Q assessments were not necessarily completed on the same day, as informants had a window of several days in which to complete the NPI-Q.

repetitive motor conditions, skin condition or sensitivity) contraindications were excluded. Informants were 18+ year old, English- speaking spouses/partners ($n = 21$, 52.5%), siblings ($n = 2$, 5%), children ($n = 8$, 20%), grandchildren ($n = 1$, 2.5%), other relatives ($n = 1$, 2.5%) or friends ($n = 7$, 17.5%) who regularly interact (in-person or remote) with the participants at least once a week. All participants and informants provided informed consent. It is important to note that informants were not necessarily caregivers; many people living with MCI including those in this study do not have a formal caregiver, particularly those showing preserved activities of daily living as required in this study. While we did not collect data on whether informants were living with participants (see Discussion), we did measure how often informants interacted with participants. 25 informants (62.5%) reported that they interacted with participants 'several times a day' (the highest frequency option provided), and 5 informants (12.5%) answered for each of the following: 'at least once a week', 'several times per week', and 'at least once daily'. This suggests that the majority of informants had very regular contact with their associated participants.

Measures

In the present study, informant-reported NPS were measured using NPI (long-form; before and after the intervention) and NPI-Q (short-form; weekly during the intervention), and participant self-reported internal states were measured using indices of valence and arousal (at the beginning of each intervention session).

NPI is a questionnaire designed to assess neuropsychiatric symptoms among individuals at risk for or with dementia (Cummings et al., 1994). It examines 12 domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, nighttime behavioral disturbances, and appetite/eating abnormalities. In this study, the informant-report NPI was used. In our study, informants were asked about the presence of each symptom in the participant. If they indicated the participant had displayed that symptom in the past 4 weeks, then they were asked a series of follow-up questions about more specific symptomology, the frequency and severity of the symptom, and the amount of distress they experienced from the participant's symptom. The presence of NPS within a domain were rated by the informant in terms of frequency (1–4; occasionally/less than once a week to very frequently/more than once a day) and symptom severity (1–3; mild to severe). Composite symptom domain scores (frequency × severity) were calculated for each domain. Informant distress was rated for each positive NPS domain (0–5; no distress to extreme distress). Total NPI score was calculated as the sum of the 12 domain scores (0–144). Informant distress level is excluded from the total NPI score.

NPI-Q is a shortened version of the NPI in which the informant indicates whether the participant exhibits symptoms in each of the 12 symptom domains. NPI-Q omits symptom frequency, based on the finding that severity is more clinically significant to caregiver distress than frequency (Kaufer et al., 2000), and severity correlates strongly with frequency (Cummings et al., 1994). The total severity (0–36) and distress (0–60) scores represent the sums of the individual severity and distress symptom scores, respectively. Symptom severity and informant distress are rated on the same respective scales used in the standard NPI. As this study was aimed at understanding the relationship between NPS measures and valence/arousal, we were interested in understanding the extent to which the NPI-Q measures each aspect of affective state. This would help us understand whether associations were likely to be driven by shared measurement variance between the NPI-Q and valence/arousal measures. Three independent raters coded each question of the NPI-Q as predominantly related to arousal or valence, and inter-rater reliability and descriptive analyses were carried out (see Results).

Self-assessment manikin (SAM) was used to assess valence and arousal (Bradley & Lang, 1994). SAM is a non-verbal, five-point pictorial scale that measures a person's affective status. Participants were asked to rate how positive vs. negative (valence) and activated vs. deactivated (arousal) they felt in the immediate moment. Higher values indicate more positive valence or higher levels of arousal. To assess the validity of this measure in our participants with MCI, we performed bivariate correlations between mean levels of arousal and valence across intervention sessions, and the participant-reported Geriatric Depression Scale (GDS)-30, which is validated in people living with MCI (Debruyne et al., 2009). We found significant negative correlations (more positive valence/higher arousal related to less severe depression symptoms) for both valence ($r(37) = -0.40$, $p = .01$) and arousal ($r(37) = -0.42$, $p = .008$), suggesting both measures are valid for detecting mood-related symptoms, and that arousal and valence are related to depressive symptoms to a similar degree.

Analysis

Measures of affective state were available from 39 participants, and NPS related measures were available from 39 informants. One participant withdrew themselves from the control group of the intervention study due to fluctuations in medication.

Relationships between corresponding measures of valence and arousal (P or P') across 14 intervention sessions (Session assessment, i) were analyzed using Generalized Estimating Equation (GEE) with AR (1) covariance correlation matrix, considering linear relationships:

$$P_i = P'_i + \text{Group} + \text{Session assessment} + \varepsilon$$

Similar GEE analysis was conducted using assessment data (weekly-w; monthly-m) to evaluate the relationship between the NPI-Q or NPI and each specific component of affect (P) from the corresponding session. Caregiving stress from NPI-Q (NPI-QC) or NPI (NPIC) was controlled. For monthly assessment, measures of participant affective state were from the first and last intervention session.

$$\text{NPI-Q}_w = P_w + \text{Group} + \text{Weekly assessment} + \text{NPI} - \text{QC}_w + \varepsilon$$
$$\text{NPI}_m = P_m + \text{Group} + \text{Monthly assessment} + \text{NPIC}_m + \varepsilon$$

Given the parent study was an intervention study, we controlled for 'Group' assignment (intervention vs. control group) throughout all analyses.

Results

Relationships between components of affect within the intervention period

Controlling for group and intervention sessions, there was a significant association between participant- reported valence and arousal ($B = 0.64$, SE = 0.06, Wald's $\chi^2 = 122.23$, $p < .001$) across

the 14 intervention sessions. Using the equation found in Rosenberg (2010), this effect size suggests arousal and valence share ~22% of variance in our sample. This is slightly larger than the ~11% seen in a large sample in the United States, but is well within the same order of magnitude (Yik et al., 2022), and similarly suggests that while related, arousal and valence capture a large amount of distinct information about participant affective state.

Relationships between components of affect and NPS within the intervention period

Controlling for group, intervention week, and caregiving distress, there were significant associations between week-to-week participant-reported arousal ($B = -0.59$, SE = 0.27, Wald's $\chi^2=4.61$, $p=.032$), but not valence ($B = 0.17$, SE = 0.19, Wald's $\chi^2=0.80$, $p=.37$), and the informant-reported NPI-Q over the four intervention sessions. This indicates that in weekly assessments in which informants reported participants as having lower levels of NPS on the NPI-Q, participants self-reported higher arousal, but not valence, during the corresponding intervention session.

Relationships between components of affect and NPS before and after intervention period

Controlling for group, monthly assessment timepoint, and caregiving distress, there was a significant association between arousal ($B = -4.00$, SE = 1.58, Wald's $\chi^2=6.42$, $p=.011$), but not valence ($B = -3.34$, SE = 1.80, Wald's $\chi^2=3.43$, $p=.06$), and informant-reported NPI at the corresponding pre- and post- intervention assessments. This suggests that for participants that reported higher levels of arousal, but not valence, their informants reported that they had lower levels of NPS on the NPI at the corresponding assessment session (i.e. first intervention session with pre-intervention assessment and last intervention session with post-intervention assessment).

Sensitivity analyses

To better understand how different moderators affected these relationships between informant-reported NPS and participant-reported affective state, we performed several analyses in specific subgroups of participants. These analyses are exploratory and should be interpreted with caution. Given the importance of gender differences in understanding emotion, we repeated the analyses controlling for gender and in males/females separately. The association between arousal and both NPI and NPI-Q remained similar when controlling for gender. The relationships between arousal and both NPI and NPI-Q were stronger in analyses including only male compared to only female participants (male, NPI: Wald's $\chi^2=10.68$, $p=.001$, NPI-Q: Wald's $\chi^2=4.11$, $p=.043$; female, NPI: Wald's $\chi^2=2.41$, $p=.12$, NPI-Q: Wald's $\chi^2=2.99$, $p=.08$). All within-gender analyses showed weak effects when using valence as the dependent variable (male, NPI: Wald's $\chi^2=0.16$, $p=.69$, NPI-Q: Wald's $\chi^2=0.18$, $p=.67$; female, NPI: Wald's $\chi^2=1.83$, $p=.33$, NPI-Q: Wald's $\chi^2=1.49$, $p=.22$).

We also compared ratings of NPI, NPI-Q, NPI caregiving distress, or NPI-Q caregiving distress between informants with different relationships to the participant. Specifically, we coded as spouse/partner (52.5%) and other. There were no significant differences in informant ratings of NPS severity or informant distress using the NPI at either time points between these two subgroups (t(38)s all < 0.765, p-values all > .451). We repeated analyses with informant type as a confound and found the relationship between NPI or NPI-Q with arousal remained similar. We also repeated analyses within each informant group: the relationships between arousal and both NPI and NPI-Q were similar in magnitude to the overall effect for the subgroup with spouse/partner as informant, but were weaker when others were used as informant (spouse/partner, NPI: Wald's $\chi^2=5.45$, $p=.020$, NPI-Q: Wald's $\chi^2=3.36$, $p=.070$; other, NPI: Wald's $\chi^2=3.39$, $p=.067$, NPI-Q: Wald's $\chi^2=0.00$, $p=.999$). Within-informant type analyses showed weak effects for valence (spouse/partner, NPI: Wald's $\chi^2=2.24$, $p=.13$, NPI-Q: Wald's $\chi^2=0.27$, $p=.61$; female, NPI: Wald's $\chi^2=0.87$, $p=.35$, NPI-Q: Wald's $\chi^2=2.37$, $p=.12$).

Finally, to understand whether the different relationships between arousal and valence, and NPS was related to measurement variance (i.e. whether the NPI was measuring valence or arousal to a greater extent), we had three independent raters code the NPI-Q questions as either measuring valence or arousal. Coders agreed upon a definition of arousal and valence based on the SAM, with arousal measuring a person's level of activation versus deactivation or calm, and valence measuring a positive/pleasant to negative/unpleasant dimension. Interrater reliability analysis showed good overall agreement (Fleiss'$\kappa=.67$, SE = 0.167, $p<.001$). On questions where there was a complete consensus (all three raters agreed: 9/12 questions overall), four were rated as measuring valence and five arousal (see Supplementary Table 1). Of the remaining three questions, two were predominantly rated as measuring valence, one arousal. This analysis suggests that NPS as measured by the NPI-Q captures both arousal and valence to similar extents, suggesting the differences between associations with arousal and valence are not driven by unequal measurement variance.

Discussion

In this study, we found that participant-reported arousal, but not valence, was significantly related to corresponding informant-reported NPS measures at both pre- and post-intervention, and weekly assessments throughout a 4-week intervention. Our sensitivity analyses suggested that the findings related to arousal were more robust in male rather than female participants, and when informants were spouses/partners of the participants. Valance showed no significant associations with NPS in any analyses. These finding suggest that informants may be responding more to participant' arousal levels than valence levels when rating their NPS, meaning that they may be under-reporting a vital piece of information about participant's affective state. Assessment of the NPI-Q by three independent raters suggested that these results are not driven by greater conceptual overlap of the NPI-Q with either valence or arousal.

Overall, the findings in this study are indicative of a disconnect between the inner experiences of people living with MCI and the perception of NPS by an informant. Within the NPI or NPI-Q the informant is asked about multiple symptoms which are related to participant affect, such as dysphoria, depression and anxiety (Wada-Isoe et al., 2020), yet participant-reported valence does not correlate with informant-report NPS. Arousal levels appeared to have a greater influence on informant reports, potentially indicating that informants may be more aware of behavioral difficulties in people living with MCI on days when they are noticeably low on arousal. This appears to be particularly the case in males, in females there was no association with

either participant- reported valence or arousal and informant-reported NPS. In this study, about half of informants were spouses of the participants, whereas the other half were other family members or friends. The relationships between arousal or fatigue with NPI or NPI-Q remained for the subgroup with spouse/partner as the informant, but not with others as the informant. It has been found that the informant-participant relationship may modulate informant ratings on subjective matters such as quality of life (Lin et al., 2017), thus it follows that informant-participant relationships would also affect informant ratings on NPS. People living with MCI might express their emotions differently to different people depending on their individual relationship with that person. Additionally, the proximity of the informant to the person living with MCI is often different between spousal relationships and other family relationships or friendships. Although we did not measure whether informants were living with participants, spouses are generally more likely to be living together with the person on which they are informing and therefore may have a different perception of symptoms than others do. Living with the person means the spouse is likely to see more of their NPS and its variability. Future studies that collect both type of relationship and proximity are needed to understand whether the spousal relationship is unique. The lack of correspondence for female participants may indicate there are gender-related differences in informant experience and perception. In this case the informants for female subjects were predominantly male spouses. Previous literature has documented that male caregivers report lower levels of experienced caregiver burden than female caregivers, especially when comparing husbands verses wives who are caregivers for their spouses (Pöysti et al., 2012). Other studies have shown that there are distinct sex-based differences in emotional perception and that women typically have superior trait empathy to men (Filkowski et al., 2017; Tracy & Giummarra, 2017). Thus, in the present study the lack of correlation between informants' (mostly male spouses) reports of NPS and the female participant's self- reported affective states may indicate that male informants are less attuned to the internal affective states of people living with MCI. Future studies are needed that more precisely measure and analyze informant interactions with participants to understand which specific elements of the informant-caregiver relationship seem to be related to these differences.

There are several open questions from this research. First, we cannot exclude the possibility that the disconnect observed in the study was due to the psychometric properties of the NPI, instead of informants' observation itself. Compared to the NPI, the Mild Behavioral Impairment Checklist seems to more accurately extract informants' observation toward subtle behavioral changes that often occur in people living with MCI (Hu et al., 2022; Ismail et al., 2017; Mallo et al., 2018). Follow-up studies should assess whether these relationships hold for alternate measures and in different clinical populations. Additionally, our rating analysis revealed that certain NPI dimensions reflect arousal and valence to different extents. Future research in larger samples should attempt to understand whether these relationships between aspects of affect and informant-reported NPS are predominantly driven by specific NPS symptom dimensions. While the use of an intervention design allowed us to better understand the dynamic relationships between NPS and participant affective state, future research may need to establish whether these findings hold for participant-reported affective state in their daily lives. Symptom reports are known to decrease in accuracy as AD progresses and meta-cognitive abilities become impaired (Cosentino & Stern, 2005). Our participants living with MCI were relatively early in disease progression, but future research with objective and covert measures of affective state (e.g. autonomic measures) may be needed to validate participant-reports of their own internal affective state, and whether these differ for arousal and valence and show similar relationships to informant-reported NPS. Finally, more research is needed to fully understand other potential moderators of informant bias in NPS assessments, including co-morbidity of psychiatric/neurological disorders, changes in AD/MCI-associated primary symptoms, or medication type and stability. A significant limitation of our study is that it has a very limited sample size that makes the assessment of these potential moderators difficult, as well as making our findings highly tentative. Future studies in larger, more diverse samples will hopefully be able to replicate and extend our findings to better understand the relationship between informant-reported NPS and participant-reported affective states. These studies should also measure whether informants are living with participants, which will enable a clearer understanding of whether being a spouse or just increased proximity to people living with MCI affects informant-reports.

Disclosure statement

The authors declare no conflicts of interest.

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