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Time of Day Effects on Inhibitory Functioning: Cognitive and Neural Evidence of Sundowning in Amnestic Mild Cognitive Impairment

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Abstract.
Background: Amnestic mild cognitive impairment (aMCI), a prodromal phase of Alzheimer's disease (AD), is characterized by episodic memory dysfunction, but inhibitory deficits have also been commonly reported. Time of day (TOD) effects have been confirmed in 1) healthy aging on cognitive processes such as inhibitory control, and 2) on behavior in AD (termed the sundowning effect), but no such research has addressed aMCI.
Objective: The present study examined the impact of TOD on the behavioral and electrophysiological correlates of inhibition in 54 individuals with aMCI and 52 healthy controls (HCs), all of morning chronotype.
Methods: Participants were randomly assigned to complete two inhibition tasks (Go-NoGo and Flanker) during their optimal (morning) or non-optimal (evening) TOD, while electroencephalography was recorded.
Results: Both tasks elicited changes in N2 and P3 event-related potential (ERP) components, which commonly index inhibitory functioning. Analyses showed that the Go-NoGo difference in P3 amplitude was reduced in individuals with aMCI relative to HCs. Compared to HCs, the Flanker difference in P3 amplitude was also reduced and coincided with more errors in the aMCI group. Notably, these behavioral and ERP differences were exaggerated in the non-optimal TOD relative to the optimal TOD.
Conclusion: Findings confirm the presence of inhibition deficits in aMCI and provide novel evidence of sundowning effects on inhibitory control in aMCI. Results reinforce the need to consider the influences of TOD in clinical assessments involving individuals with aMCI.

Keywords: Amnestic mild cognitive impairment, circadian rhythms, chronotype, executive functions, Flanker task, Go-NoGo task

INTRODUCTION

Inhibitory control, a key component of executive functions, refers to the abilities to suppress automatic but inappropriate responses, and to withstand

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interference from irrelevant or distracting stimuli [1–3]. This core cognitive process is critical for goal-directed behavior in everyday life [4]. For example, on a daily basis, this might translate into difficulties inhibiting unwanted reactions or impulses (e.g., blurting out comments without thinking) or ignoring distractions in your environment (e.g., attending to irrelevant noises or actions of nearby co-workers). The real-world consequences of distraction are particularly evident in older adults, as age-related impairments in attentional control have been linked to a greater risk of falls [5, 6], traffic accidents [7, 8], and driver errors [9, 10].

Inhibitory control is commonly divided into two subtypes: response inhibition and interference control [11, 12]. Response inhibition reflects the suppression of a pre-potent or automatic response (as is required in the Go-NoGo task; [13]), and interference control reflects the capacity to filter out distracting information that has been partially activated but irrelevant to the task at hand (as is required in the Flanker task; [14]). In the Go-NoGo task, individuals have to withhold a response to infrequent stimuli (NoGo trials) among a set of standard stimuli (Go trials). For the Flanker task, individuals have to disregard distractor arrows flanking a centre arrow, with distractor arrows pointing in the same direction (i.e., congruent trials) or different direction (i.e., incongruent trials) of the target.

Several studies have used time-locked electroencephalographic activity or event-related potentials (ERPs) to investigate inhibitory processes in Go-NoGo and Flanker paradigms for two key reasons. First, the high temporal resolution of ERPs ideally quantifies the dynamic and rapidly occurring neural activity in cognitive processes like inhibitory control [15, 16]. Secondly, ERPs provide the opportunity to measure neural activity even when successful inhibition is indexed by the lack of a behavioral response, such as on NoGo trials (i.e., withholding a prepotent motor response on no-response trials) in the Go-NoGo task [17].

The electrophysiological correlates of inhibition most commonly viewed in Go-NoGo and Flanker tasks are the N2 and P3 components. The N2 is a negative-deflecting ERP waveform at approximately 250–400 ms post-stimulus onset [18–22]. N2 amplitude is now a recognized ERP index of conflict detection [23, 24]. N2 amplitude in the Go-NoGo task has been shown to be bigger for NoGo than Go trials [25–27]. The N2 in the Flanker task has been shown to be larger in amplitude and longer in latency for incongruent relative to congruent trials [20, 28–32]. Past work has confirmed that response inhibition and interference control share comparable early cognitive resources [33]. That is, the N2 in Go-NoGo tasks is thought to reflect conflict stemming from competition between the implementation and inhibition of responses in Go relative to NoGo trials [23, 24]. In the Flanker task, it is thought to reflect conflict arising from distracting flankers surrounding the target [32, 34].

The P3 is a centroparietally distributed, positive-going ERP waveform that occurs around 300 to 600 ms following stimulus onset. This component is believed to represent later-stage monitoring of inhibitory control processes and is tied to inhibition of the motor response [35, 36] and the effectiveness of the inhibitory response [37–39]. P3 latency and amplitude are modulated by fluctuating demands for motor suppression and inhibition. In the Go-NoGo task, P3 amplitude is larger for NoGo than Go trials [40, 41]. In the Flanker task, the P3 has a smaller amplitude [42] and longer latency [43, 44] for Incongruent relative to Congruent trials. Kan and colleagues [33] showed that interference control and response inhibition, evaluated by a hybrid Go-NoGo Flanker task, share comparable cognitive processes in the initial stages (i.e., N2), but display differential temporal mechanisms in the later stages of inhibitory processing (i.e., P3). The Go-NoGo P3 signifies the active suppression of the motor response [45, 46] and the Flanker P3 signifies the inhibition and resolution required to negotiate the conflict response demands of the target stimulus [47, 48].

Given the importance of inhibitory control for goal-directed behavior in everyday life, an extensive body of research has focused on declines in inhibitory functioning in older adults with mild cognitive impairment (MCI) [49–54]. MCI is a transitional phase between normal aging and dementia. Persons with MCI exhibit a decline in cognition greater than expected based on age, but are able to preserve functional independence [55].

Of particular interest to the current study is inhibitory deficits in the MCI subtype known as amnestic MCI (aMCI). aMCI is a prodromal stage of dementia due to Alzheimer's disease (AD), albeit it can progress to other types of dementia [56]. While episodic memory deficits are considered a hallmark of aMCI, deficits in inhibitory control are also quite common [57–59]. A meta-analysis by Rabi and colleagues [53] including 2,184 individuals with aMCI and 3,049 healthy controls (HCs) found aMCI-

related deficits of moderate effect size (Hedge's $g = -0.73$) on behavioral measures of inhibitory control including deficits in both response inhibition and interference control. Prior work using Go-NoGo tasks has shown aMCI-related behavioral deficits in response inhibition as reflected by higher error rates [60–64; but see 65]. Additionally, past studies using Flanker tasks have found aMCI-related deficits in interference control as reflected by greater accuracy and RT differences between congruent and incongruent trials[1] [66–71; but see 72]. Using the same sample of participants as used in the current study, Chow et al. [50] reported greater intraindividual variability (i.e., within-person variability in performance across trials) in both Go-NoGo and Flanker RTs in those with aMCI compared to controls. The current study extends the findings of Chow et al. [50] by considering neural indices of inhibition in aMCI, in addition to behavioral indices.

When compared to behavioral research, ERP research involving inhibitory control in aMCI is rather limited. N2 amplitudes in the Go/NoGo task have been shown to be smaller in individuals with aMCI relative to healthy controls [60, 61, 73]. Research examining Go-NoGo latency effects have observed longer N2 latencies in individuals with aMCI relative to HCs reflecting aMCI-related slowing, but no P3 latency group effects [62]. Among the other research, NoGo-N2 and P3 latencies did not differ between individuals with aMCI and healthy controls [60, 61, 64].

López-Zunini and colleagues [64] demonstrated that individuals with aMCI exhibited smaller P3 amplitudes in both Go and NoGo conditions than healthy controls. Furthermore, using a Go-NoGo task with an auditory distraction component, Cid-Fernandez and colleagues [60, 61] also found smaller N2 amplitudes in both Go and NoGo conditions in those with aMCI compared to controls. However, as N2 and P3 modulation effects (difference between Go and NoGo waveforms) index inhibition [74], these past findings may instead reflect more general attention deficits in aMCI, rather than response inhibition deficits per se. Indeed, prior research has yet to demonstrate N2 or P3 modulation effects in aMCI on the Go-NoGo task, either because no effect was found [62, 64] and/or because within-condition differences (Go versus NoGo, or the Go-NoGo effect) were not examined [60, 61].

Only one study to our knowledge has examined ERP indices of inhibition in the Flanker task among individuals with aMCI. Wang and colleagues [72] found that individuals with aMCI were less accurate across conditions relative to HCs. However, no difference in behavioral measures of inhibition (i.e., RT and accuracy differences between incongruent versus neutral trials) were observed between the aMCI and HC groups. Reduced N2 and P3 amplitudes were reported in all Flanker conditions in individuals with aMCI relative to HCs; however, no N2 and P3 modulation effects were found, suggesting more generalized attentional deficits in aMCI. Wang et al. [72] also observed longer N2 latencies in the aMCI group relative to the HC group, suggesting slower neural processing in aMCI.

While ERP research using the Flanker task in aMCI remains limited, additional ERP work has investigated interference control in aMCI using different tasks (i.e., Stroop task and Simon task). Ramos-Goicia et al. [75] demonstrated that cognitive status did not impact behavioral Stroop performance, but they found greater P3 modulation (i.e., difference between incongruent and control conditions) in individuals with aMCI relative to HCs. Cespón et al. [77] used the Simon task and showed higher error rates in aMCI, with smaller N2 amplitudes and longer N2 latencies in aMCI versus HCs [76–78]. These findings suggest greater interference due to distraction in those with aMCI relative to controls, which is also reflected in delayed and diminished allocation of neural activity associated with interference control.

Inhibitory control efficiency changes throughout the day depending on synchronization of endogenous circadian rhythms [79]. The *synchrony effect* denotes the interaction between time of day (TOD) and chronotype, and implicates improved performance for optimal relative to non-optimal TOD [79]. Chronotype norms vary among different age groups, with most older adults being morning types (i.e., optimal performance during the morning hours) [79–81]. Most relevant to the current study, Rabi and colleagues [74] studied the effects of TOD and aging on the neural correlates of inhibition in the Flanker and Go-NoGo tasks with the same sample of healthy older adults as in the current study. While behavioral results revealed no effects of TOD, Rabi et al. [74] found synchrony effects in ERP indices of response inhibition, demonstrating greater Go-NoGo modulation of N2 amplitude and P3 amplitude during non-optimal

[1]The Borsa et al., 2016, Van Dam et al., 2013, and Zhang et al., 2015 studies refer to the Flanker component of the Attention Network Task.

compared to optimal test sessions. Additionally, older adults showed greater Flanker P3 amplitude modulation than younger adults, but only during non-optimal testing times. The current study examines whether there are neural indications of impaired inhibition in aMCI, beyond those identified in healthy aging by Rabi et al. [74].

TOD effects have also been demonstrated in individuals with AD, with an exacerbation of symptoms in the late afternoon and evening, termed the *sundowning effect* [82, 83], and circadian rhythm disturbances have been reported in MCI [84, 85]. Among individuals in the milder stages of AD, frequently reported symptoms in the evening hours include confusion, poor inhibition, and memory decline [82, 86]. Sundowning has been explained as a type of circadian dysfunction linked to changes in daily body temperature rhythms [83]. However, no studies to date have examined the effects of TOD and aMCI on inhibitory control. Recent work by Wilks and colleagues [87] used a remotely administered smartphone assessment to sample cognition over several days among individuals at risk for AD and controls. Findings revealed no difference from morning to evening performance on memory and processing speed measures within at-risk individuals. However, there was a strong trend for at-risk individuals to perform worse in the evening hours compared to morning hours. TOD conclusions from this study are encouraging, but limited, as Wilks et al. did not assess inhibitory control in their study, only 10% of their sample were classified as at-risk, there was no assessment of chronotype, and participants self-selected hours they wished to complete the assessments. If inhibition deficits are exaggerated during the later afternoon and evening hours among individuals with aMCI, this could have important implications for clinical management.

The main goal of this study was to examine how TOD modulates behavioral and ERP measures of two inhibition tasks between individuals with aMCI and controls, to establish to what extent cognitive sundowning effects are present in preclinical AD. A Go-NoGo task was included to assess response inhibition and a Flanker task was included to assess interference control. To examine the effects of TOD (optimal or non-optimal) and cognitive status (HC or aMCI) on inhibitory control, we recruited older adults with morning chronotypes who were randomized to either morning (optimal TOD) or late-afternoon/evening (non-optimal TOD) testing sessions. Electroencephalography (EEG) was used to record neuroelectric activity during inhibition tasks to examine how TOD impacts the N2 and P3 ERP components differentially in those with aMCI compared to healthy controls.

In line with prior behavioral work examining inhibitory control in aMCI [50, 53, 60–64, 66, 67, 70], we hypothesized that individuals with aMCI would show poorer response inhibition and interference control compared to HCs. This would be reflected by larger accuracy and reaction time difference scores between a simple processing condition and an inhibitory control condition. Consistent with prior work showing reduced N2 and P3 amplitudes across conditions in both Go-NoGo and Flanker tasks [60, 61, 64, 72], we anticipated individuals with aMCI would show smaller modulation of N2 and P3 ERP components, suggesting impaired inhibitory processing. Lastly, given recent work using the same sample of healthy older adults, where more pronounced TOD effects in older adults relative to younger adults on ERP measures of inhibitory control were found [74], and based on prior work highlighting circadian dysfunction in early AD [84–86], we expected more pronounced aMCI-related differences in inhibitory control on behavioral and neural indices of inhibition during the non-optimal TOD compared to HCs.

METHODS

Participants

Participant recruitment followed the same exclusion criteria as previously reported in Chow et al. [50] and Rabi et al. [74], which included screening for diagnosis of neurological or psychiatric disorders, vascular disorders, head injury, and visual and hearing impairment. Inclusion criteria were 60 years of age or older, a score above the cut-off on the Telephone Interview for Cognitive Status-Modified (TICS-M) [88], and classified as morning-type individuals. The Morningness-Eveningness Questionnaire (MEQ) [89] was used to ensure participants were of the morning chronotype, scoring at or above 59. The validity of the MEQ has been verified through associations with circadian-linked changes including heart rate, body temperature, and skin conductance [89–91].

Fifty-four HCs and 59 individuals with aMCI were recruited for the study. Using Petersen's 2004 [55] criteria, participants were diagnosed by a registered neuropsychologist (N. D. Anderson) according to a) memory complaint, b) objective memory impairment verified by neuropsychological assessment, and c)

maintenance of a functional level of independence in daily activities. Impairment was operationalized as an age-corrected scaled score 1.5 standard deviations below the participant's estimated intellectual functioning on two or more tests within a cognitive domain. As previously reported by Chow et al. [50] and Rabi et al. [74], data were excluded from analysis for two participants with aMCI and one HC who did not complete the inhibition tasks; and two participants with aMCI who received a diagnosis of another neurological disorder after testing. To control for the effects of sleep disturbances on inhibitory performance [92], data were excluded from one HC participant who reported insufficient sleep the night before testing. Our final sample consisted of 52 HCs (64–88 years, 25 females), with 26 tested during the optimal TOD, and 26 tested during the non-optimal TOD; and 54 individuals with aMCI (66–88 years, 26 females), with 28 tested during the optimal TOD and 26 tested during the non-optimal TOD.

Participants were recruited from the Rotman Research Institute research participant database, the Sam and Ida Ross Memory Clinic of Baycrest Centre, and through local advertisements and community talks. This study was approved by the Research Ethics Board of the Rotman Research Institute at Baycrest Centre, and all participants provided informed written consent.

Neuropsychological assessment

A full description of the administered neuropsychological assessments have been previously reported in Chow et al. [50] and Rabi et al. [74], All neuropsychological assessments were conducted during an individual's optimal TOD (9:00 to 12:00). Participants were administered measures of global cognitive ability, memory, language, and executive function, in addition to abbreviated estimates of fluid and crystalized intelligence. Several self-report questionnaires were administered to evaluate quality of sleep, mood functioning, and subjective memory concerns. Functional independence was assessed through self-report questionnaires and verified with a reliable third-party informant.

Procedure

Participants performed both inhibition tasks on a separate day than the neuropsychological assessment. Participants were randomized to complete their inhibition tasks either in the morning (i.e., optimal TOD; started tasks between 8:00–10:30, with the study completed by 12:00), or in the afternoon (i.e., non-optimal TOD; started tasks between 14:00–17:00 start time, with the study completed by 18:30). The order in which the inhibition tasks were administered were counterbalanced across participants in the study. Participants completed both inhibition tasks in a double-walled sound-attenuated booth while seated 60 cm in distance from the monitor, with stimuli at a visual angle of 2.9 degrees for the Go-NoGo task, and stimuli at a visual angle of 3.8 degrees for the Flanker task.

Computer tasks

The present study adopted the Go-NoGo paradigm used and reported by Moussard et al. [93]. Geometrical shapes were presented one at a time on a computer monitor. To reduce stimulus repetition effects, four stimuli were generated from two types of shapes (squares or triangles) and two colors (pink or white). A colored shape was presented on a black background for 186 ms followed by a fixed blank screen interstimulus interval lasting 1500, 2000, or 2500 ms to prevent expectancy effects. To control for stimulus saliency, assignment of stimulus colors to Go and NoGo stimuli was counterbalanced across individuals in the study. Participants were asked to press the keyboard spacebar quickly and accurately in response to Go stimuli (75% probability) and to avoid responding to NoGo stimuli (25% probability). Participants had 1000 ms from the onset of the stimulus to make a response and were given 20 practice trials to familiarize themselves with the task. The task included three blocks, consisting of 192 trials in each block. There were 576 trials in total (432 Go and 144 NoGo trials).

Details of the Flanker task were previously reported in our work [50, 74]. Five stimuli were presented centered horizontally on a computer, with each array consisting of a centered arrowhead pointing either to the left or right, and two flanker arrowheads on either side of the central arrowhead. All five of the arrowheads were pointing in the same direction in Congruent arrays (e.g., >>>>>) and four flanking arrowheads were pointing in the direction opposite of the central arrowhead in Incongruent arrays (e.g., >><>>). The central arrowhead was flanked by four equal signs in Neutral arrays (e.g., = =>= =). A stimulus array was presented in black on a white background for 300 ms followed by a fixed interstimulus interval of 2000 ms with a central fixation cross. Participants were asked to quickly and accurately press

the arrow key on the computer keyboard that corresponded to the direction of the central arrowhead. The left index finger was used to respond to central arrowheads facing left, and the right index finger was used to respond to central arrowheads facing right. The window to respond was 2300 ms from stimulus onset. There were three blocks in the task (102 trials each), with 306 trials in total (102 trials per condition). Participants were given 17 practice trials to familiarize themselves with the task.

Task stimuli were presented using E-Prime software version 1.2 (Psychology Software Tools, Inc.). No feedback to participants was provided concerning their performance.

EEG acquisition and preprocessing

EEG was recorded from 66 Ag/AgCI scalp electrodes (BioSemi ActiveTwo acquisition system, BioSemi V.O.F., Amsterdam, Netherlands), using the 10-20 system, a common mode sense active electrode, with a right leg passive electrode as ground. Ten facial electrodes were used to monitor eye movements (placed at both mastoids, both pre-auricular points, outer canthus of each eye, inferior orbit of each eye, and two additional frontotemporal electrodes). EEG activity was recorded at a rate of 512 Hz using a bandpass of DC-100 Hz. Brain Electrical Source Analysis software (BESA Research, version 7.0, MEGIS GmbH, Gräfelfing, Germany) was used for off-line preprocessing.

For ERP analyses, the average of all scalp EEG channels was used as the reference for each EEG channel. Continuous EEG data were filtered with 0.53 Hz high-pass (forward, 6 dB/octave) and 40 Hz low-pass filters (zero-phase, 24 dB/octave). Channels with excessive head or body movement artifacts were interpolated using spherical spline interpolation [94]. No more than 10% of the channels per recording were interpolated. Artifacts from eye movements were corrected based on the spatial components approach [95]. Brain signal topographies underlying eye movements and eye blinks were semi-automatically detected per participant recording, then the artifact signal for each electrode was reconstructed with a spatial filter and modeled by a fixed dipole model [95]. The spatial topographies were then subtracted from the continuous EEG.

The next step involved segmenting the data for each participant into epochs of -500 ms to 1000 ms with a baseline of -500 ms to 0 ms. The ERP analysis included only correct trials. Traces were scanned for additional artifacts and epochs including deflections surpassing a 120 μV were marked and excluded from the analysis. An average of 7.58% ($SD = 6.81\%$) of trials per participant were removed in the Go-NoGo task and 5.40% ($SD = 5.00\%$) of trials per participant in the Flanker task, neither of which varied by group, $F(1, 102) = 0.17$, $p = 0.682$, $\eta_p^2 = 0.002$, and $F(1, 102) = 0.236$, $p = 0.628$, $\eta_p^2 = 0.002$, respectively. This also did not vary by TOD for the Go-NoGo task, $F(1, 102) = 0.375$, $p = 0.542$, $\eta_p^2 = 0.004$; for the Flanker task, a slightly greater proportion of trials per participant were excluded in the Non-Optimal (6.46% on average) compared to the Optimal TOD (4.44% on average), $F(1, 102) = 5.07$, $p = 0.027$, $\eta_p^2 = 0.047$. The remaining epochs were averaged according to task conditions, and averaged epochs were baseline-corrected relative to the pre-stimulus interval (i.e., mean amplitude over the 500 ms prior to onset of the stimulus). Waveforms for the Go-NoGo task included a mean of 402.66 Go trials ($SD = 40.50$) and 123.32 NoGo trials ($SD = 18.05$) per participant; for the Flanker task, these were 95.72 ($SD = 10.41$) Congruent, 84.87 ($SD = 14.33$) Incongruent, and 95.48 ($SD = 10.26$) Neutral trials analyzed.

Data preparation

Behavioral measures. Accuracy from the Go-NoGo task was derived from hits and correct rejections. RTs from this task were computed from only Go trials (hits). In the Flanker task, trials with no response were removed from accuracy calculations. Additionally, to account for task warm-up effects, the first trial in each block was omitted from analyses. Trials with a response time of less than 200 ms were also removed from analyses. This removed on average 0.07% ($SD = 0.16\%$) of trials per participant in the Go-NoGo task, and 0.04% ($SD = 0.15\%$) of trials per participant in the Flanker task, neither of which varied by group ($F(1, 102) = 0.13$, $p = 0.722$, $\eta_p^2 = 0.001$ and $F(1, 102) = 3.24$, $p = 0.075$, $\eta_p^2 = 0.031$, respectively) or TOD ($F(1, 102) = 1.15$, $p = 0.287$, $\eta_p^2 = 0.011$ and $F(1, 102) = 0.01$, $p = 0.905$, $\eta_p^2 < 0.001$, respectively). Flanker task accuracy was calculated for the Congruent, Incongruent, and Neutral conditions. Mean RT was derived using trials with correct responses, and any trials with an RT that was 3 standard deviations or more from the participants' mean in each condition were removed. This removed on average 1.14% ($SD = 0.58\%$) of Go trials per participant in the Go-NoGo task, which did not vary by group, $F(1,$

102) = 0.02, $p = 0.899$, $\eta_p^2 < 0.001$, or TOD, $F(1, 102) = 0.45$, $p = 0.504$, $\eta_p^2 = 0.004$. In the Flanker task, this removed on average 1.31% ($SD = 0.69\%$) of trials per participant, which did not vary by group, $F(1, 102) = 0.21$, $p = 0.649$, $\eta_p^2 = 0.002$, or TOD, $F(1, 102) = 0.32$, $p = 0.570$, $\eta_p^2 = 0.003$.

ERP measures. The effects of TOD and aMCI on the neural indices of inhibition (N2 and P3 mean amplitudes and peak latencies) were assessed using a mixed model ANOVA with Group (HC, aMCI) and TOD (optimal, non-optimal) as between subject factors, and Condition (Incongruent, Neutral, Congruent for Flanker; Go and No-Go for Go-NoGo) as the within-subjects factor. Peak latencies were quantified as the maximum positivity or negativity within a particular window for an electrode cluster. For both inhibition tasks, the N2 was maximal at frontal-central regions, and was thus averaged across a cluster of nine electrodes in the frontal-central scalp region to better represent the N2 distribution (F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2). For both inhibition tasks, the P3 was maximal at central to centro-parietal regions, and was similarly averaged across a cluster of nine central electrodes (FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2).

N2 peak latencies from each task were exported per individual at the latency of the maximal negative-going peak between a liberal search window of 200 to 400 ms post stimulus onset. P3 peak latencies from each task were determined for each individual at the maximal positive-going peak between a liberal search window of 300 to 650 ms post stimulus onset. Upon visual inspection, N2 mean amplitudes were derived from a time window of 250-350 ms for the Go-NoGo task and 225-350 ms for the Flanker task. P3 mean amplitudes for both tasks were derived using a 350-600 ms time window. These time windows are consistent with those previously used in our OA sample as reported in Rabi et al. [74].

Data analysis

Behavioral measures. Statistical analysis of behavioral data was performed using SAS/STAT software version 15.2 and the SAS System for Windows version 9.4. Copyright © 2016 SAS Institute Inc. To accommodate the positively skewed distribution of RT, generalized linear mixed models (GLMMs) for gamma distribution (with an identity link) were used to model the individual trial RT data [93]. A random intercept and a variance component structure were used to control for the non-independence of the data.

Accuracy data were fitted to a modified Poisson model [96], which estimates the proportion correct and ratios of proportions correct across groups. The model used a compound symmetry type working correlation matrix and generalized estimating equations to adjust for the repeated measures within subjects.

The models were adjusted for sex, age, and education. The initial model included the interaction of all fixed effects for each outcome. The model was simplified to contain only significant interactions and related main effects or only main effects when no interaction terms were significant. The fixed effects included: Group (HC, aMCI), TOD (Optimal, Non-Optimal), and condition (Go-NoGo Task: Go, No-Go; Flanker Task: Incongruent, Neutral, Congruent).

An initial gamma GLMM model was fit without any fixed effects (an intercept model only) for reaction time data. The standard deviation of the predicted mean RT was used as the denominator of effect size calculations for differences in mean RT. Effect sizes were interpreted according to Cohen's d criteria [97]; an effect size of 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect.

ERP measures. ERP analyses were conducted using IBM SPSS (version 28.0) and JASP (version 0.16) software. Electrophysiological measures were submitted to analyses of covariance (ANCOVA) with age, sex, and education as covariates, and Sidak post-hoc tests to adjust for multiple comparisons. N2 and P3 peak latencies and mean amplitudes from the Go-NoGo task were submitted to a mixed ANCOVA with Group (HC, aMCI) as a between-subjects factor and Condition (Go, NoGo) as a within-subjects factor. For the Flanker task, N2 and P3 peak latencies and mean amplitudes, were subjected to a mixed ANCOVA with Group (HC, aMCI) as a between-subjects factor and Condition (Congruent, Incongruent, Neutral) as a within-subjects factor. When a 3-way interaction reached significance, post-hoc two-way ANCOVAs were used to investigate Flanker effects (i.e., difference between Incongruent and Congruent/Neutral). Partial eta-squared was calculated as measures of effect sizes. A Greenhouse-Geisser correction was used for violations of sphericity. An alpha value of 0.05 was used throughout.

In line with our prior work [74], the difference between Go and NoGo, or between Incongruent and Congruent/Neutral (i.e., amplitude modulations) were taken as a measure of the Go-NoGo or Flanker

effect reflecting inhibitory processing. To confirm that N2 and P3 amplitude modulations were associated with inhibition in HCs and individuals with aMCI, partial bivariate Pearson correlations were performed between ERP and behavioral measures of inhibition while controlling for the same covariates (age, sex, and education). Correlations were conducted between N2 or P3 modulations and behavioral performance. Given that peak latencies assess slowing of neural processing rather than inhibition, correlations were not conducted with this measure.

RESULTS

Participant characteristics

The subgroups did not statistically differ in age, $F(3, 102) = 1.10$, $p = 0.353$, $\eta_p{}^2 = 0.031$, or sex, $\chi^2(3, N = 106) = 0.984$, $p = 0.157$. A Kruskal-Wallis H test showed that the subgroups differed in education, $\chi^2(3) = 8.02$, $p = 0.046$, with greater years of education in the HC non-optimal TOD subgroup (17.12 years, $SD = 2.55$) than the aMCI optimal TOD subgroup (14.93 years, $SD = 2.83$), $p = 0.049$. However, education did not differ between the HC optimal TOD (15.88 years, $SD = 3.01$) and HC non-optimal TOD subgroups ($p = 0.182$) or between aMCI optimal and non-optimal TOD (16.12 years, $SD = 2.72$) subgroups ($p = 0.107$). Importantly, the subgroups also did not differ in education level within levels of TOD. Specifically, education did not significantly differ between the aMCI optimal and HC optimal TOD subgroups ($p = 0.145$), nor did it differ between aMCI non-optimal and HC non-optimal TOD subgroups ($p = 0.237$). A Kruskal-Wallis H test showed that the subgroups did not differ on MEQ score, $\chi^2(3) = 5.75$, $p = 0.124$.

Behavioral results

Go-NoGo performance. Age was the only significant covariate, with lower accuracy for older participants. There were no differences in Go-NoGo accuracy between groups or TOD assignment (see Supplementary Tables 1 and 2), and for this reason the model was simplified to include only the Condition main effect. As depicted in Fig. 1, participants made more errors on NoGo than Go trials, $\chi^2(1) = 52.87$, $p < 0.001$, *accuracy ratio* = 0.910, indicating a ~9% decrease in NoGo accuracy relative to Go accuracy across groups.

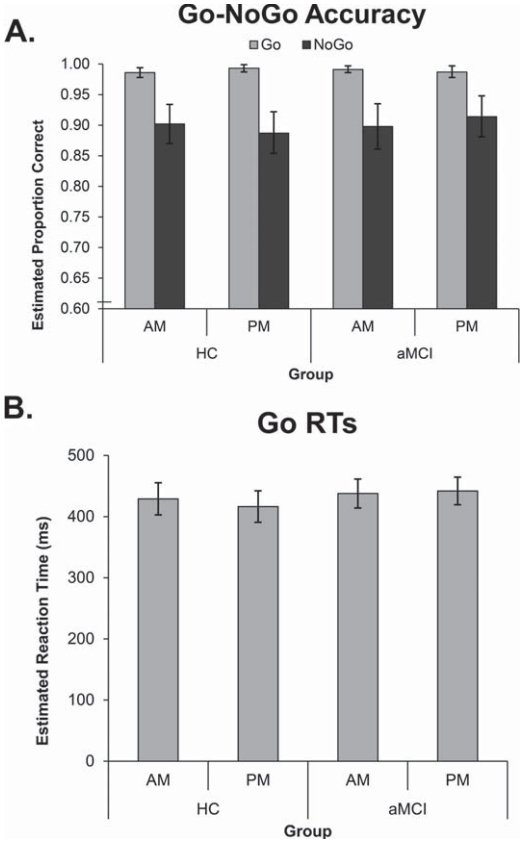

Fig. 1. Go-NoGo task performance displayed by group, TOD, and condition for measures of (A) accuracy, and (B) mean RT. For visualization purposes, data depicted represents models with a 3-way interaction for Go-NoGo accuracy and a 2-way interaction for Go RT, rather than the final simplified models. Error bars represent 95% confidence intervals, and the y-axis scale for accuracy is truncated to aid in visualizing the Go-NoGo effect. RT, reaction time. The estimates presented are with reference to males with average age and education.

There were no significant covariates related to Go RTs and an intercept-only model was considered sufficient (see Supplementary Table 1).

Flanker performance. Flanker behavioral results are displayed in Fig. 2. TOD did not influence accuracy on the Flanker task (see Supplementary Tables 3 and 4), and so the model was simplified to Group, Condition, and their interaction. Type III tests for fixed effects indicated accuracy was comparable for HCs and individuals with aMCI, $\chi^2(1) = 2.02$, $p = 0.155$, and differed across Condition, $\chi^2(2) = 53.61$, $p < 0.001$, in the model with a significant Group and Condition interaction, $\chi^2(2) = 7.94$, $p = 0.019$. Individuals with aMCI had lower accuracy in the Incongruent condition, compared to both the Congruent condition (*accuracy*

Table 1
Participant characteristics and neuropsychological test scores

Variable	HC Optimal TOD ($n = 26$)		HC Non-Optimal TOD ($n = 26$)		aMCI Optimal TOD ($n = 28$)		aMCI Non-Optimal TOD ($n = 26$)	
	Raw	Scaled	Raw	Scaled	Raw	Scaled	Raw	Scaled
Demographics								
Age (y)	75.15 (7.38)	–	75.23 (5.40)	–	77.57 (6.49)	–	77.27 (6.01)	–
Education (y)	15.88 (3.01)	–	17.12 (2.55)	–	14.93 (2.83)	–	16.12 (2.72)	–
Sex (F:M)	12:14	–	13:13	–	14:14	–	13:13	–
TICS-m[a]	37.42 (2.76)	–	36.96 (3.29)	–	32.25 (3.18)	–	33.62 (2.80)	–
MEQ	65.96 (4.79)	–	65.65 (4.66)	–	64.25 (5.35)	–	63.31 (4.04)	–
MoCA[a]	26.92 (2.42)	–	26.88 (2.39)	–	22.46 (2.24)	–	22.81 (3.20)	–
Estimates of IQ								
WAIS-III Matrix Reasoning[a]	24.46 (3.80)	14.54 (2.23)	24.04 (5.59)	14.31 (2.62)	20.57 (4.70)	13.11 (2.39)	21.65 (6.93)	13.42 (3.11)
Shipley Vocabulary[a,c]	35.46 (2.98)	12.00 (2.24)	36.19 (3.68)	12.96 (3.14)	32.82 (3.98)	10.14 (2.84)	36.04 (2.78)	12.65 (2.50)
Memory								
CVLT-II Learning[a]	49.28 (9.06)	13.08 (2.29)	50.12 (14.63)	13.77 (3.29)	24.70 (8.50)	5.33 (2.75)	26.62 (9.24)	6.08 (2.74)
CVLT-II Short Delay FR[a]	10.52 (3.33)	12.52 (3.24)	10.27 (3.56)	12.12 (3.15)	2.63 (2.32)	4.22 (2.67)	2.48 (2.77)	3.80 (3.49)
CVLT-II Long Delay FR[a]	10.40 (3.32)	11.36 (2.86)	10.92 (3.62)	11.85 (2.89)	2.69 (2.28)	4.00 (2.73)	2.88 (2.68)	4.20 (2.95)
WMS-R Visual PA I[a]	12.36 (3.34)	12.00 (2.66)	11.92 (3.58)	11.81 (2.53)	7.86 (3.96)	9.25 (2.44)	7.73 (4.13)	9.04 (2.57)
WMS-R Visual PA II[a]	5.04 (1.40)	11.84 (1.75)	5.12 (1.37)	12.15 (1.46)	2.89 (1.81)	9.75 (2.24)	3.35 (1.98)	10.08 (2.33)
WMS-R Verbal PA I[a]	15.72 (3.37)	9.60 (2.24)	17.11 (2.98)	10.88 (2.44)	9.75 (3.33)	5.32 (2.52)	10.54 (4.44)	6.00 (2.97)
WMS-R Verbal PA II[a]	6.92 (1.04)	11.84 (1.84)	7.00 (1.17)	12.00 (2.47)	4.46 (1.64)	8.14 (2.68)	4.54 (2.20)	8.77 (3.46)
WAIS-III Digit Symbol IL-FR[a]	7.58 (1.06)	10.54 (0.99)	7.42 (1.21)	10.38 (1.33)	4.71 (2.12)	7.46 (3.20)	5.08 (1.90)	7.92 (2.87)
WAIS-III Digit Symbol IL-PR[a]	12.58 (4.37)	10.50 (1.36)	12.73 (4.37)	10.65 (1.02)	4.50 (4.33)	6.86 (3.42)	3.96 (4.60)	6.35 (3.68)
Language								
BNT-15[a]	53.60 (5.77)	10.80 (3.33)	54.08 (3.77)	11.12 (2.70)	48.07 (9.23)	8.82 (2.98)	51.08 (7.27)	10.38 (3.42)
Phonemic Fluency (FAS)[a]	48.58 (13.31)	12.00 (3.00)	49.88 (13.17)	12.04 (3.56)	37.07 (11.78)	9.39 (3.20)	43.12 (9.80)	10.54 (2.76)
Semantic Fluency (Animals)[a]	17.54 (4.45)	9.81 (2.80)	19.46 (5.09)	10.81 (3.70)	12.25 (4.53)	6.14 (3.16)	14.19 (3.46)	7.50 (2.53)

(*Continued*)

Table 1
(*Continued*)

Variable	HC Optimal TOD ($n = 26$)		HC Non-Optimal TOD ($n = 26$)		aMCI Optimal TOD ($n = 28$)		aMCI Non-Optimal TOD ($n = 26$)	
	Raw	Scaled	Raw	Scaled	Raw	Scaled	Raw	Scaled
Executive Functioning and Processing Speed								
WAIS-III Digit Symbol[d]	57.96 (13.82)	12.23 (2.80)	65.58 (14.75)	13.69 (2.99)	51.68 (16.31)	11.21 (3.02)	47.15 (15.02)	10.19 (2.79)
D-KEFS Trails Numbers[b]	37.87 (10.72)	12.85 (2.09)	39.27 (15.45)	12.88 (2.41)	52.53 (19.89)	11.21 (3.51)	51.81 (29.77)	11.31 (3.65)
D-KEFS Trails Letters[b]	36.56 (10.06)	12.96 (1.43)	40.49 (13.89)	12.63 (1.84)	55.17 (20.9)	10.93 (2.97)	53.36 (31.77)	11.32 (3.30)
D-KEFS Trails N-L Switch[b]	95.13 (36.85)	12.27 (2.05)	94.51 (44.80)	12.35 (2.81)	148.70 (62.72)	9.00 (4.63)	146.43 (77.14)	9.19 (4.94)
D-KEFS CWIT Colour [b]	30.31 (5.89)	11.58 (2.22)	30.88 (4.85)	11.42 (1.93)	34.85 (8.31)	10.00 (3.28)	35.33 (9.31)	9.72 (3.60)
D-KEFS CWIT Word	23.51 (5.11)	11.21 (2.64)	22.31 (4.77)	11.88 (2.36)	25.31 (6.92)	10.48 (3.14)	25.02 (5.80)	10.44 (2.93)
D-KEFS CWIT Inhibition[b]	58.61 (15.17)	12.88 (2.07)	56.78 (9.17)	13.08 (1.35)	73.80 (23.08)	11.11 (2.86)	80.53 (37.07)	10.32 (4.18)
Alpha Span SP[a]	27.68 (9.58)	10.12 (2.99)	30.04 (11.97)	11.08 (3.67)	20.74 (6.95)	8.33 (2.77)	20.69 (7.70)	8.35 (3.01)
WCST Categories[a]	4.81 (1.96)	–	5.00 (1.62)	–	3.64 (2.39)	–	3.85 (2.38)	–
WCST Perseverative Errors %[b]	14.35 (10.04)	13.52 (4.74)	14.15 (10.28)	12.92 (4.53)	24.55 (14.72)	9.93 (4.29)	22.27 (13.55)	10.35 (4.27)
Questionnaires								
HADS Anxiety	5.08 (3.31)	–	4.08 (2.33)	–	5.56 (4.01)	–	5.62 (3.95)	–
HADS Depression	2.12 (1.90)	–	2.70 (2.00)	–	3.15 (2.46)	–	3.58 (2.66)	–
EPW[a]	6.60 (2.89)	–	7.50 (3.18)	–	5.19 (3.56)	–	6.04 (3.95)	–
PSQI	5.92 (3.46)	–	6.16 (2.53)	–	5.44 (3.16)	–	5.08 (2.67)	–
MAC Abilities[a]	68.75 (9.65)	10.71 (2.26)	70.20 (9.61)	10.96 (2.44)	59.96 (10.81)	8.36 (2.70)	58.12 (7.59)	7.85 (1.97)
FAQ	–	–	–	–	2.22 (2.21)	–	1.77 (2.32)	–

Data are means (SDs) except for sex. HC, healthy control; aMCI, amnestic mild cognitive impairment; MoCA, Montreal Cognitive Assessment; TICS-m, modified Telephone Interview of Cognitive Status (raw score out of 50); MEQ, Morningness-Eveningness Questionnaire; WAIS, Wechsler Adult Intelligence Scale; WMS-R, Wechsler Memory Scale – Revised; CVLT, California Verbal Learning Test; FR, Free Recall; PA, Paired Associates; IL, Incidental Learning; PR, Paired Recall; BNT, Boston Naming Test; FAS, phonemic fluency to the letters F, A, and S; D-KEFS, Delis Kaplan Executive Functioning System; N-L, Number-Letter; CWIT, Color Word Interference Test; SP, Stop Point; WCST, Wisconsin Card Sorting Test; HADS, Hospital Anxiety and Depression Scale; EPW, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; MAC, Memory Assessment Clinics Self-Rating Scale; FAQ, Functional Assessment Questionnaire. For normed assessments, tests of significance were run on scaled scores. The same sample of healthy older adults was used in the Rabi et al. [74] study. [a]HC > aMCI, [b]HC < aMCI, [c]Non-Optimal>Optimal, [d]HC Non-Optimal>aMCI Non-Optimal.

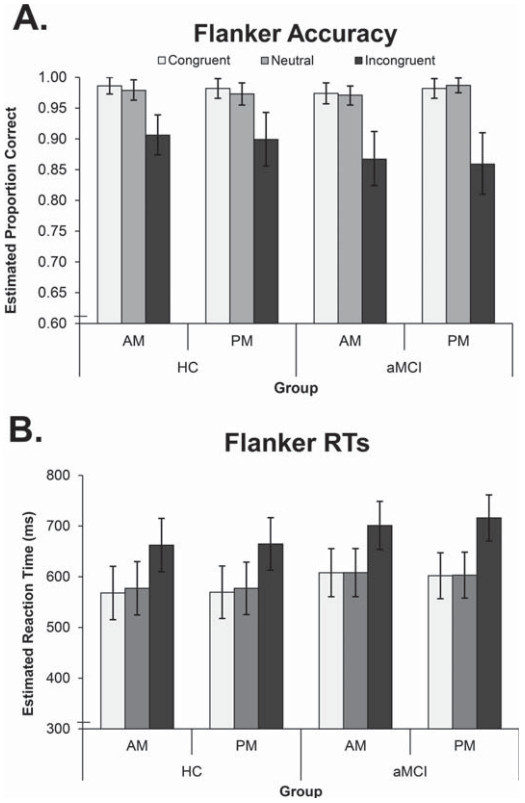

Fig. 2. Flanker task performance displayed by group, TOD, and condition for measures of (A) accuracy, and (B) mean RT as illustrated by the final models. Error bars represent 95% confidence intervals. RT, reaction time. The estimates presented are with reference to males with average age and education.

ratio = 0.883, $p < 0.001$) and the Neutral condition (*accuracy ratio* = 0.882, $p < 0.001$). HCs also had lower accuracy in the Incongruent condition, compared to both the Congruent condition (*accuracy ratio* = 0.917, $p < 0.001$) and the Neutral condition (*accuracy ratio* = 0.924, $p < 0.001$). The relative accuracy ratio (aMCI versus HC) was significant for the incongruent compared to neutral condition comparison (*relative accuracy ratio* = 0.954, $p = 0.03$) indicating relatively poorer accuracy for the aMCI group in the incongruent trials. Although not significant, the aMCI group had relatively poorer accuracy for the incongruent compared to the congruent condition (*relative accuracy ratio* = 0.963, $p = 0.09$).

The model for Flanker RTs (see Supplementary Tables 3 and 5) included TOD, Group, Condition, and their 2- and 3-way interactions. Type III tests for fixed effects indicated RTs differed across conditions, $F(2, 29203) = 2985.64$, $p < 0.001$, and both the Group by Condition, $F(2, 29203) = 17.53$, $p < 0.001$, and TOD by Condition, $F(2, 29203) = 9.50$, $p < 0.001$, interactions were significant. These were all modified by a significant 3-way Group x TOD x Condition interaction, $F(2, 29203) = 7.11$, $p < 0.001$. In HCs, both the Incongruent-Congruent effect (*effect size*$_{\text{inc-con}} = 0.005$, $p = 0.841$) and the Incongruent-Neutral effect (*effect size* $_{\text{inc-neu}} = 0.016$, $p = 0.529$) did not differ as a function of TOD. By contrast, individuals with aMCI showed larger Flanker effects (i.e., a bigger difference between inhibition and control conditions) during the non-optimal TOD relative to optimal TOD. During the non-optimal TOD, individuals with aMCI showed both a larger difference between incongruent and congruent conditions (*effect size* $_{\text{inc-con}} = 0.137$, $p < 0.001$), as well as incongruent and neutral conditions (*effect size* $_{\text{inc-neu}} = 0.129$, $p < 0.001$), relative to the optimal TOD.

To summarize, Group and TOD modulated inhibition performance on the Flanker task, such that the aMCI group showed greater Flanker effects in accuracy and RTs than the HC group. Notably, Flanker effects in RTs in the aMCI group were greater in the non-optimal than optimal TOD. No Group or TOD effects were found in the Go-NoGo task.

Go-NoGo ERP results

N2. Figure 3 displays the Go-NoGo ERP findings. Analyses revealed no significant main effects or interactions involving Group, TOD, or Condition on N2 latency or mean amplitude. Furthermore, the Go-NoGo N2 modulation was not significantly correlated with the Go-NoGo effect in accuracy for either group (both $p > 0.05$).

P3. Latency analyses revealed no significant main effects or interactions involving Group, TOD, or Condition. The analysis for P3 mean amplitudes revealed a significant Group by Condition interaction, $F(1, 99) = 4.02$, $p = 0.048$, $\eta_p{}^2 = 0.039$, with a significantly greater P3 amplitude modulation in the HC group than the aMCI group ($p = 0.048$). As expected, P3 amplitudes were greater in NoGo than Go trials for both HC ($p < 0.001$) and aMCI ($p = 0.002$) groups. No other interaction involving Group, Condition, or TOD reached significance. The Go-NoGo P3 modulation was not significantly correlated with the Go-NoGo effect in accuracy for either group (both $p > 0.05$).

Summary. No group or TOD effects were demonstrated for the Go-NoGo N2. The aMCI group demonstrated a smaller P3 amplitude modulation than the HC group.

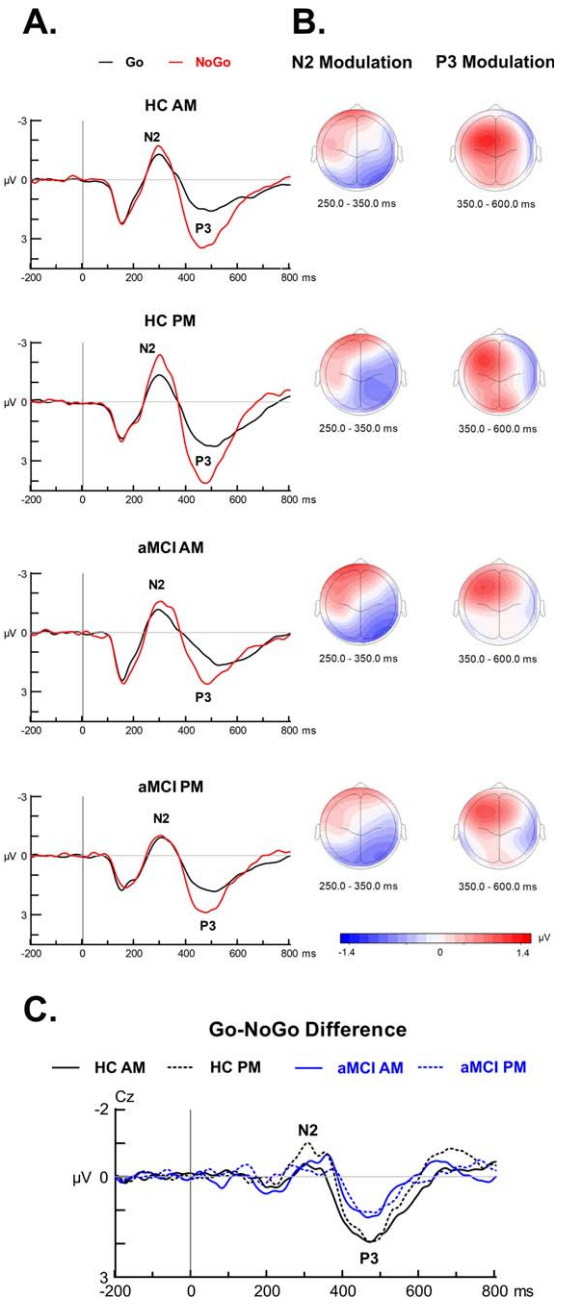

Fig. 3. Go-NoGo grand average waveforms, and difference waveforms at the central midline electrode (Cz) for brevity. A) Representative grand-average waveforms for Go and NoGo trials across the four subgroups depicting N2 and P3 components. B) Topographical scalp maps of the Go-NoGo effect, and C) difference waveforms (NoGo minus Go) depicting the N2 and P3 components across the four subgroups.

Flanker ERP results

N2. Figure 4 displays the Flanker ERP findings. N2 latency revealed a significant Condition by TOD interaction, $F(2, 198) = 3.32$, $p = 0.038$, $\eta_p^2 = 0.032$. During the optimal TOD, Neutral N2 latencies were significantly longer than Incongruent ($p < 0.001$) and Congruent ($p < 0.001$) trials, with no significant difference between Incongruent and Congruent trials ($p = 0.999$). During the non-optimal TOD, N2 latencies did not differ between conditions (all $p > 0.05$). N2 latencies were not significantly different between TOD for Incongruent ($p = 0.095$), Congruent ($p = 0.308$) or Neutral trials ($p = 0.989$). No other effects reached significance ($p > 0.05$).

N2 mean amplitudes differed as a function of condition, $F(1.93, 191.39) = 3.77$, $p = 0.026$, $\eta_p^2 = 0.037$. However, no pairwise comparisons reached significance (all $p > 0.05$). No other interactions involving Group, Condition, or TOD reached significance. A greater Flanker N2 modulation was correlated with a greater Flanker effect in RTs for the HC group (Incongruent-Congruent: $r = 0.286$, $p = 0.046$; Incongruent-Neutral: $r = -0.289$, $p = 0.044$) and for the aMCI group[2] (Incongruent-Neutral: $r = 0.291$, $p = 0.039$).

P3. Flanker P3 latency analyses revealed a significant Group by Condition interaction, $F(1.55, 153.37) = 3.90$, $p = 0.032$, $\eta_p^2 = 0.038$. Simple main effects analyses by Condition revealed significantly longer P3 latencies for Incongruent trials in the aMCI group than the HC group ($p = 0.012$); latencies did not significantly differ between groups for Congruent ($p = 0.386$) or Neutral trials ($p = 0.416$). No other effects reached significance ($p > 0.05$).

For Flanker P3 mean amplitudes, the 3-way Group by Condition by TOD interaction reached significance, $F(1.52, 150.81) = 3.38$, $p = 0.049$, $\eta_p^2 = 0.033$. Post-hoc analyses revealed, in the non-optimal TOD, a greater Incongruent-Neutral P3 modulation in the HC group than the aMCI group ($p = 0.001$), whereas this modulation did not significantly differ between group in the optimal TOD ($p = 0.449$). Furthermore, in the non-optimal TOD, the Incongruent-Congruent P3 modulation was also greater in the HC group than the aMCI group ($p = 0.003$), whereas this modulation was not significantly different between groups in the optimal TOD ($p = 0.437$). In the HC group, a greater P3 amplitude modulation was correlated with a greater Flanker effect in RTs (Incongruent-Congruent: $r = 0.511$, $p < 0.001$; Incongruent-Neutral: $r = 0.382$, $p = 0.007$). In the

[2]Flanker N2 modulation was not correlated with a Flanker effect in RTs when comparing Incongruent-Congruent trials in aMCI ($p = 0.085$).

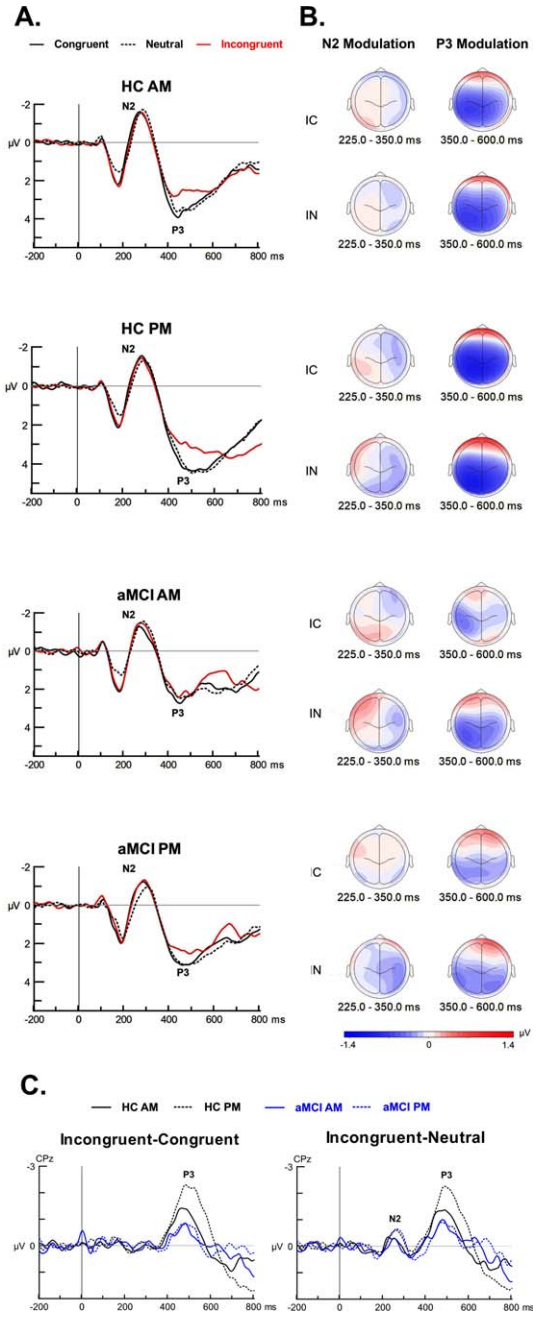

Fig. 4. Flanker grand average waveforms and difference waveforms at the central midline electrode (Cz) for brevity. (A) Representative grand-averaged waveforms for Congruent, Incongruent, and Neutral trials across the four subgroups. The N2 and P3 waves are depicted, and (B) topographical scalp maps for both Flanker interference effects are presented to the right of the grand-averaged waveforms (IC, Incongruent minus Congruent; IN, Incongruent minus Neutral). C) Difference waveforms (Incongruent minus Congruent and Incongruent minus Neutral) showing the N2 and P3 modulations at the Cz electrode across the four subgroups.

aMCI group, the P3 modulation did not significantly correlate with inhibition performance ($p > 0.05$ for all).

Summary. ERP peak latency measures revealed group and TOD differences in neural processing of inhibition: Flanker N2 latencies modulated with TOD, which did not vary by group; Flanker P3 latencies modulated with group but did not vary by TOD. In ERP mean amplitude measures, the aMCI group demonstrated a smaller Flanker P3 amplitude modulation than the HC group in the non-optimal TOD, but not in the optimal TOD. This P3 modulation was correlated with performance on the Flanker task in the HC group, but not in the aMCI group.

DISCUSSION

The present study investigated the influences of aMCI and TOD on response inhibition and interference control using behavioral and electrophysiological measures. Both behavioral and electrophysiological findings demonstrated TOD differences in interference control whereas these were not shown with response inhibition. Individuals with aMCI showed interference control deficits (as indexed by larger Flanker RT effects) and altered neural processing (as indexed by reduced Flanker P3 amplitude modulation) relative to controls. Both findings were exaggerated during the non-optimal afternoon-to-evening testing times, compared to their optimal TOD in the morning.

Response inhibition

Behavioral measures of Go-NoGo task performance revealed only condition differences in Go-NoGo accuracy, with participants committing more errors on NoGo relative to Go trials. Contrary to our predictions, no differences in RT or accuracy were found between groups. Variations in task designs and complexity (such as Go-NoGo tasks with additional auditory distraction [60, 61] or with semantic categorization [62]) may explain why some prior research has demonstrated behavioral deficits in aMCI, while the present study did not find such effects.

ERP latency measures confirmed no group-related or TOD-related slowing of N2 and P3 latency, suggesting no aMCI-related deficits or circadian-mismatch deficits in neural processing speed among participants with aMCI. With the exception of Mudar et al. [62] who observed longer N2 latencies in individuals with aMCI, our results are consistent with

other studies showing no such differences in N2 and P3 latencies on Go-NoGo tasks [60, 61, 64].

Although individuals with aMCI have demonstrated smaller N2 and P3 amplitudes than controls across both Go and NoGo conditions [60, 61, 64], prior research has yet to demonstrate N2 or P3 amplitude modulation effects on response inhibition measures [62, 64]. Similarly, we too did not observe any N2 modulation effects between groups or TOD. However, for the first time to our knowledge, we show a greater P3 amplitude modulation in HCs relative to individuals with aMCI on the Go-NoGo task. This P3 amplitude modulation in the absence of behavioral deficits suggests that differences in response inhibition between aMCI and HC groups may be most evident at the later processing stages (i.e., action execution/suppression) relative to the earlier stages (i.e., conflict monitoring). We argue that our difference-wave approach better isolates ERP components of interest in a more process-pure manner, and therefore extends prior literature showing general attenuations in P3 amplitude across task conditions in those with aMCI compared to controls [64]. Furthermore, the current findings provide evidence for aMCI-related differences in neural activity underlying response inhibition, but these differences were not strong enough to elicit behavioral differences in our response inhibition task.

Interference control

In agreement with prior literature demonstrating larger Flanker interference effects in aMCI [66–71], individuals with aMCI made more errors than HCs on the incongruent condition compared to the congruent and neutral conditions, suggesting that individuals with aMCI show deficits in processes associated with interference control. Furthermore, while controls did not demonstrate any RT interference effects as a function of TOD, individuals with aMCI showed larger Flanker RT effects (between incongruent-congruent and incongruent-neutral trials) during the non-optimal TOD relative to optimal TOD. For the first time to our knowledge, our findings signify that individuals with aMCI encounter greater difficulty resolving conflict during periods of circadian mismatch than do HCs. Our current results suggest that interference control deficits in aMCI are more apparent during non-optimal hours; individuals with aMCI may more likely overcome inhibitory processing challenges in the morning.

Flanker ERP findings in the current study did not show any N2 modulation effects between groups or TOD. These findings are consistent with Wang and colleagues [72], who found reduced N2 amplitudes across conditions (indexing attentional deficits) in those with aMCI, but no N2 modulation effects between incongruent and control conditions in the aMCI group. Our findings also suggest the presence of TOD effects in N2 latency. Across groups, neutral N2 latencies were delayed relative to incongruent and congruent N2 latencies during the optimal TOD only. Given the limited ERP research examining TOD influences on cognition, this unanticipated result cannot be explained relative to prior findings and requires future research. We presume that these differential findings in N2 latency reflect additional processing of neutral stimuli during peak inhibitory functioning attributed to differences in the stimuli types (i.e., equal signs are only present in neutral trials but not incongruent or congruent trials). During off-peak times (i.e., evening hours), attentional resources may be more depleted, limiting additional processing of these neutral stimuli [98].

In support of our predictions, HCs showed a larger P3 amplitude modulation than individuals with aMCI, but only in the non-optimal TOD. Brain-behavior analyses revealed that greater P3 modulation in HCs was connected with a greater Flanker effect in RT (i.e., poorer interference control). The current findings are consistent with prior work showing TOD effects (i.e., sundowning) in AD [82–85] and TOD effects on memory in those with MCI [87], and resemble the exaggeration of differences between age groups when assessments are done during the non-optimal TOD [99]. Using the same sample of older adults, we recently reported differential P3 modulation in healthy older and younger adults as a function of TOD [74]. The current results demonstrate, for the first time, that TOD effects in interference control exist in aMCI over and above those observed in healthy aging. In sum, individuals with aMCI manifest behavioral deficits in interference control as reflected by accuracy measures. Additionally, persons with aMCI demonstrate TOD effects in interference control as reflected by behavioral deficits (i.e., larger Flanker effects in RTs) and altered neural processing (i.e., reduced P3 modulation) during the non-optimal TOD relative to optimal TOD.

Lastly, the current findings showed that Flanker P3 peak latencies for incongruent trials were delayed in

individuals with aMCI compared to HCs. This finding provides partial support for the findings of Wang et al. [72] showing longer latencies in the earlier ERP component associated with the Flanker task (N2 latency) between individuals with aMCI and HCs. While some may interpret the delayed P3 latency finding in our study as reflecting deficits in interference control processing, we instead adopt the more widely-held view that N2 and P3 latency index information processing speed and not inhibition [100–104]. Furthermore, we conclude that the delayed P3 incongruent latency in our aMCI group indexes general aMCI-related slowing.

Theoretical implications

The current study findings have key theoretical implications for the neural correlates underlying inhibition in aMCI. Past research has indicated that across inhibition tasks, the N2 indexes conflict monitoring and detection [23, 24], and the P3 differentially indexes response inhibition in the Go-NoGo task and interference resolution in the Flanker task [33, 45, 46]. Furthermore, the absence of N2 modulation effects across groups and TOD in the present study suggests differences linked to aMCI in the later, but not earlier, stages of inhibitory processing. These deficits mirror those from our prior work comparing healthy younger and older adults, showing that age-related changes in inhibition influenced the later stages (as indexed by the P3 modulation), more so than the earlier stages (as indexed by the N2 modulation) [74]. Indeed, our younger adult sample as reported in Rabi et al. [74] showed larger N2 modulations but smaller P3 modulations than healthy older adults. Not surprisingly, these age-related changes also coincided with TOD effects in the N2 modulation within younger adults, and TOD effects in P3 modulation within healthy older adults [74]. Our findings in the present paper show aMCI-related deficits in inhibitory processing above and beyond changes in inhibitory processing expected in healthy aging. As our study was the first to show P3 modulation differences between individuals with aMCI and HCs, future research is needed to clarify P3 modulation effects in aMCI as prior research has either failed to find such an effect [62, 64, 72], failed to examine such effects [60, 61], or too limited research has been conducted on the topic (in the case of ERP components of interference control in aMCI).

In the present study, the differential P3 modulation seen across groups in both tasks coupled with the decline in Flanker behavioral performance among individuals with aMCI confirm the presence of altered neural inhibitory processing and interference control deficits in aMCI. One potential explanation for these findings is neuroimaging evidence of aMCI as a type of disconnection syndrome. Prior research has identified a subset of brain regions frequently activated across inhibitory control subtypes. This includes the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC), brain regions that have also been tied to aMCI-related pathology [24, 105–110]. Compared to HCs, persons with aMCI display reduced parietal connectivity with the DLPFC, highlighting a disconnection between anterior and posterior brain regions and a functional disconnection within a distributed frontal-parietal network [111, 112]. The functional disconnection present in aMCI may further clarify deficits seen in executive functioning, which depend on distributed networks connecting different brain regions. Core executive functions like inhibitory control are dependent upon prefrontal brain regions, and atrophy of the prefrontal cortex, altered prefrontal activation patterns, and increased beta amyloid deposition in the prefrontal cortex have all been identified in aMCI [113–116]. These alterations in the neural network responsible for inhibitory control may explain the behavioral and neural processing differences seen among individuals with aMCI relative to HCs in the present study.

Finally, our finding of differential group and TOD effects on tasks assessing different inhibitory control subtypes has important theoretical implications. That is, for our response inhibition measure (i.e., Go-NoGo task), differential neural processing was evident in the aMCI group relative to HC group, but behavioral deficits between groups or TOD were not found. In contrast, multiple measures from behavioral and neural indices of interference control on the Flanker task showed group and TOD differences. While neural processing differences were found between groups on the Go-NoGo task, the absence of behavioral deficits or TOD differences may suggest that response inhibition is more spared in aMCI relative to interference control. In support of this viewpoint, Zhang et al. [65] failed to detect group differences between those with aMCI and HC participants on their Go-NoGo task. Additionally, the magnitude of TOD effects have been shown to vary based on the inhibitory control sub-

type assessed in healthy aging [117]. Results showed that older adults tested in the evening but not morning, showed higher Stroop interference effects than younger adults; however, no such effects were demonstrated in a secondary inhibitory control task involving negative priming.

For several reasons, a more likely explanation for our Go-NoGo findings is that differences in neural activity underlying inhibition were present, but these differences were not strong enough to elicit behavioral differences. While more complex tasks are likely to uncover behavioral deficits on response inhibition measures [53, 60–64], our behavioral response inhibition ceiling effect maybe beneficial to understanding neural functioning and neurodegeneration in aMCI. That is, our differential P3 amplitude modulation finding in the absence of behavioral deficits highlights neural differences due to intrinsic characteristics of the groups (i.e., aMCI pathology), unconfounded by differences in task difficulty.

Clinical implications

Results from the current study support the presence of interference control deficits and alterations in the neural mechanisms of inhibition in aMCI. Such findings support the use of ERP indices of inhibitory control as early biomarkers of cognitive decline in aMCI. Particularly in the case of response inhibition, findings showcase the sensitivity of ERP to detect group differences in the absence of behavioral differences, again reinforcing the potential utility of ERP indices like the P3 as an early screening tool for aMCI (see [52] for a review of the use of cognitive ERPs in MCI).

Given that behavioral findings in the current study clearly showed interference control deficits in aMCI, it is our recommendation that tasks like the Flanker task should be regularly included in neuropsychological assessments to fully capture cognitive dysfunction. Additionally, our findings highlight the strength of using computer tasks to assess inhibitory performance. While untraditional to neuropsychological assessment, mounting evidence has revealed the effectiveness of computer-based neuropsychological assessment tools like the NIH EXAMINER and NIH TOOLBOX, especially given that these methods can provide more accurate measurements of RT [118–121].

The current findings showcase how the behavioral and neural correlates of inhibitory control begin to deteriorate during prodromal stages of AD, which can ultimately assist clinicians and researchers with prognosis and inform early intervention design. Thus far, interventions have been implemented addressing memory deficits in aMCI [122–126], but less so for executive function deficits in aMCI [127, 128]. As outlined by Zhao et al. [128], previous cognitive training studies involving persons with MCI did not dedicate sufficient training of executive functions [129, 130]. Furthermore, individuals with aMCI may benefit from training interventions focused on improving inhibition in the context of memory paradigms, similar to what has been implemented in healthy older adults [131, 132].

Based on the present findings showing that inhibitory control performance and neural processing/efficiency fluctuate with TOD in aMCI, this suggests that assessing inhibition performance at varying times of day may lead to misinterpretations regarding cognitive status or an aMCI diagnosis. These findings are in line with previous research showing TOD modulations in the Trail Making Test (commonly administered in neuropsychological test batteries) in healthy older adults [79] and TOD effects on a neuropsychological test battery in rehabilitation inpatients with cognitive impairment due to stroke, traumatic brain injury, and spinal cord injury [133]. The current results reinforce the clinical importance of taking TOD and chronotype into account when deciding when to administer inhibitory control tests and interventions.

Our findings suggesting the presence of cognitive sundowning in aMCI also have important implications for this population when deciding when to complete complex tasks. There is a practical benefit in informing individuals with aMCI about TOD effects so that they can better structure their day and the tasks important for everyday functioning. For example, clinicians may advise individuals diagnosed with aMCI to avoid completing tasks that are taxing on inhibitory control resources (like paying bills or driving) during non-optimal times of day (most commonly the late-afternoon to evening hours).

Limitations and future directions

The present study adopted a between-subjects design and randomly assigned participants to morning or afternoon testing sessions. Alternatively, a within-subjects design could have been used to test each participant in the morning and afternoon. This design would have removed the risk of confounding effects related to group differences and provide

a more direct comparison between each participant's performance at both their optimal and non-optimal TOD. However, a downside of using a within-subjects design is the potential for practice effects which could cloud true TOD differences. Another factor which should be considered in similar future research is aMCI subtype. As prior research has shown more pronounced inhibition deficits in multiple-domain aMCI (characterized by impairments in memory plus at least one other cognitive domain) relative to single-domain aMCI (characterized solely by memory impairments) [50, 61, 78], it follows that future research should investigate whether TOD effects on inhibitory control are more pronounced in multiple- relative to single-domain aMCI.

TOD effects were exclusively found in the interference control subtype of inhibitory control but not the response inhibition subtype. We speculate that differences in task complexity may be partially responsible for these findings and so we recommend that future research examine inhibitory control processing in aMCI using inhibition tasks of varying complexity and type. For example, to clarify the role of TOD on response inhibition performance in aMCI, a range of tasks including the Continuous Performance Task, Sustained Attention to Response Task, Hayling task, and Stop-Signal Task could be examined (see [53] for a review of inhibition tasks). Future research is also needed to clarify how deficits and altered neural processing on standard inhibitory control tasks in aMCI extends to everyday functioning. Furthermore, we did not find the N2 amplitude to vary by group or as a function of inhibitory demands in either task, whereas other studies have found group main effects for this ERP component [64,72]; this remains to be further studied. Finally, to fully understand the effects of TOD on the neural mechanisms that underlie inhibitory control in pathological aging, future research should aim to conduct longitudinal studies assessing the magnitude of cognitive sundowning effects as people progress from aMCI to AD.

Conclusion

Behavioral and neurophysiological findings from the present study highlight the effects of TOD and aMCI-related pathology on inhibitory control functioning. Individuals with aMCI demonstrated altered neural processing across inhibitory control domains. To our knowledge, we report the first study showing TOD modulations of interference control performance and neural processing in aMCI, providing novel electrophysiological support for the presence of cognitive sundowning in the preclinical stages of AD. Results from the current study reinforce the need to evaluate inhibitory control functioning in the cognitive assessment of aMCI used in neuropsychology. Additionally, our findings inform the need for TOD effects to be considered in clinical practice and research assessing cognition in aMCI to circumvent misinterpretation of test results and potential misdiagnoses during inappropriately timed neuropsychological assessments.

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Diamond A (2013) Executive functions. *Ann Rev Psychol* **64**, 135-168.

[2] Hasher L, Campbell KL (2020) Inhibitory theory: Assumptions, findings, and relevance to interventions. In *The Cambridge Handbook of Cognitive Aging: A Life Course Perspective*, Thomas AK, Gutchess A, eds. Cambridge University Press, pp. 147-160.

[3] Zacks RT, Hasher L (1994) Directed ignoring: Inhibitory regulation of working memory. In *Inhibitory Processes in Attention, Memory, and Language*, Dagenbach D, Carr TH, eds. Academic Press, San Diego, CA, US, pp. 241-264.

[4] Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev* **33**, 631-646.

[5] Amboni M, Barone P, Hausdorff JM (2013) Cognitive contributions to gait and falls: Evidence and implications: Cognitive contributions to gait and falls. *Mov Disord* **28**, 1520-1533.

[6] Mirelman A, Herman T, Brozgol M, Dorfman M, Sprecher E, Schweiger A, Giladi N, Hausdorff JM (2012) Executive function and falls in older adults: New findings from a five-year prospective study link fall risk to cognition. *PLoS One* **7**, e40297.

[7] Nagamatsu LS, Voss M, Neider MB, Gaspar JG, Handy TC, Kramer AF, Liu-Ambrose TYL (2011) Increased cognitive load leads to impaired mobility decisions in seniors at risk for falls. *Psychol Aging* **26**, 253-259.

[8] Neider MB, Gaspar JG, McCarley JS, Crowell JA, Kaczmarski H, Kramer AF (2011) Walking and talking: Dual-task effects on street crossing behavior in older adults. *Psychol Aging* **26**, 260-268.

[9] Hoffman L, McDowd JM, Atchley P, Dubinsky R (2005) The role of visual attention in predicting driving impairment in older adults. *Psychol Aging* **20**, 610-622.

[10] Thompson KR, Johnson AM, Emerson JL, Dawson JD, Boer ER, Rizzo M (2012) Distracted driving in elderly and middle-aged drivers. *Accid Anal Prev* **45**, 711-717.

[11] Nigg JT (2000) On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychol Bull* **126**, 220-246.

[12] Friedman NP, Miyake A (2004) The relations among inhibition and interference control functions: A latent-variable analysis. *J Exp Psychol Gen* **133**, 101-135.

[13] Mesulam M-M (1985) *Principles of behavioral neurology*, Oxford University Press, USA.

[14] Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys* **16**, 143-149.

[15] Albert J, López-Martín S, Hinojosa JA, Carretié L (2013) Spatiotemporal characterization of response inhibition. *Neuroimage* **76**, 272-281.

[16] Pires L, Leitão J, Guerrini C, Simões MR (2014) Event-related brain potentials in the study of inhibition: Cognitive control, source localization and age-related modulations. *Neuropsychol Rev* **24**, 461-490.

[17] Huster RJ, Messel MS, Thunberg C, Raud L (2020) The P300 as marker of inhibitory control - Fact or fiction? *Cortex* **132**, 334-348.

[18] Bartholow BD, Pearson MA, Dickter CL, Sher KJ, Fabiani M, Gratton G (2005) Strategic control and medial frontal negativity: Beyond errors and response conflict. *Psychophysiology* **42**, 33-42.

[19] Heil M, Osman A, Wiegelmann J, Rolke B, Hennighausen E (2000) N200 in the Eriksen-Task: Inhibitory executive processes? *J Psychophysiol* **14**, 218-225.

[20] Kopp B, Rist F, Mattler U (1996) N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology* **33**, 282-294.

[21] Liotti M, Woldorff MG, Perez R, Mayberg HS (2000) An ERP study of the temporal course of the Stroop color-word interference effect. *Neuropsychologia* **38**, 701-711.

[22] Yeung N, Botvinick MM, Cohen JD (2004) The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychol Rev* **111**, 931-959.

[23] Donkers FCL, van Boxtel GJM (2004) The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain Cogn* **56**, 165-176.

[24] Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR (2003) Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cogn Affect Behav Neurosci* **3**, 17-26.

[25] Falkenstein M, Hoormann J, Hohnsbein J (1999) ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychol* **101**, 267-291.

[26] Folstein JR, Van Petten C (2008) Influence of cognitive control and mismatch on the N2 component of the ERP: A review. *Psychophysiology* **45**, 152-170.

[27] Van 't Ent D, Apkarian P (1999) Motoric response inhibition in finger movement and saccadic eye movement: A comparative study. *Clin Neurophysiol* **110**, 1058-1072.

[28] Brydges CR, Clunies-Ross K, Clohessy M, Lo ZL, Nguyen A, Rousset C, Whitelaw P, Yeap YJ, Fox AM (2012) Dissociable components of cognitive control: An event-related potential (ERP) study of response inhibition and interference suppression. *PLoS One* **7**, e34482.

[29] Frühholz S, Godde B, Finke M, Herrmann M (2011) Spatio-temporal brain dynamics in a combined stimulus–stimulus and stimulus–response conflict task. *Neuroimage* **54**, 622-634.

[30] Kopp B, Mattler U, Goertz R, Rist F (1996) N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. *Electroencephalogr Clin Neurophysiol* **99**, 19-27.

[31] Mansfield KL, van der Molen MW, Falkenstein M, van Boxtel GJM (2013) Temporal dynamics of interference in Simon and Eriksen tasks considered within the context of a dual-process model. *Brain Cogn* **82**, 353-363.

[32] Vanveen V, Carter C (2002) The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol Behav* **77**, 477-482.

[33] Kan Y, Xue W, Zhao H, Wang X, Guo X, Duan H (2021) The discrepant effect of acute stress on cognitive inhibition and response inhibition. *Conscious Cogn* **91**, 103131.

[34] Zhou S, Xiong S, Cheng W, Wang Y (2019) Flanker paradigm contains conflict and distraction factors with distinct neural mechanisms: An ERP analysis in a 2-1 mapping task. *Cogn Neurodyn* **13**, 341-356.

[35] Polich J, Heine MRD (1996) P300 topography and modality effects from a single-stimulus paradigm. *Psychophysiology* **33**, 747-752.

[36] Waller DA, Hazeltine E, Wessel JR (2021) Common neural processes during action-stopping and infrequent stimulus detection: The frontocentral P3 as an index of generic motor inhibition. *Int J Psychophysiol* **163**, 11-21.

[37] Falkenstein M, Koshlykova NA, Kiroj VN, Hoormann J, Hohnsbein J (1995) Late ERP components in visual and auditory Go/Nogo tasks. *Electroencephalogr Clin Neurophysiol* **96**, 36-43.
[38] Pfefferbaum A, Ford JM (1988) ERPs to stimuli requiring response production and inhibition: Effects of age, probability and visual noise. *Electroencephalogr Clin Neurophysiol* **71**, 55-63.
[39] Roberts LE, Rau H, Lutzenberger W, Birbaumer N (1994) Mapping P300 waves onto inhibition: Go/No Go discrimination. *Electroencephalogr Clin Neurophysiol* **92**, 44-55.
[40] Bokura H, Yamaguchi S, Kobayashi S (2001) Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clin Neurophysiol* **112**, 2224-2232.
[41] Pfefferbaum A, Ford JM, Weller BJ, Kopell BS (1985) ERPs to response production and inhibition. *Electroencephalogr Clin Neurophysiol* **60**, 423-434.
[42] Hsieh S, Liang Y-C, Tsai Y-C (2012) Do age-related changes contribute to the flanker effect? *Clin Neurophysiol* **123**, 960-972.
[43] Hsieh S, Fang W (2012) Elderly adults through compensatory responses can be just as capable as young adults in inhibiting the flanker influence. *Biol Psychol* **90**, 113-126.
[44] Wild-Wall N, Falkenstein M, Hohnsbein J (2008) Flanker interference in young and older participants as reflected in event-related potentials. *Brain Res* **1211**, 72-84.
[45] Band GPH, van Boxtel GJM (1999) Inhibitory motor control in stop paradigms: Review and reinterpretation of neural mechanisms. *Acta Psychol* **101**, 179-211.
[46] Kok A, Ramautar JR, De Ruiter MB, Band GPH, Ridderinkhof KR (2004) ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology* **41**, 9-20.
[47] Scrivano RM, Kieffaber PD (2022) Behavioral and electrophysiological correlates of Simon and flanker conflict interference in younger and older adults. *Aging Neuropsychol Cogn* **29**, 318-348.
[48] Van't Ent D (2002) Perceptual and motor contributions to performance and ERP components after incorrect motor activation in a flanker reaction task. *Clin Neurophysiol* **113**, 270-283.
[49] Chiang H-S, Spence JS, Kraut MA, Mudar RA (2018) Age effects on event-related potentials in individuals with amnestic mild cognitive impairment during semantic categorization Go/NoGo tasks. *Neurosci Lett* **670**, 19-21.
[50] Chow R, Rabi R, Paracha S, Vasquez BP, Hasher L, Alain C, Anderson ND (2022) Reaction time intraindividual variability reveals inhibitory deficits in single- and multiple-domain amnestic mild cognitive impairment. *J Gerontol B Psychol Sci Soc Sci* **77**, 71-83.
[51] Guarino A, Forte G, Giovannoli J, Casagrande M (2020) Executive functions in the elderly with mild cognitive impairment: A systematic review on motor and cognitive inhibition, conflict control and cognitive flexibility. *Aging Mental Health* **24**, 1028-1045.
[52] Paitel ER, Samii MR, Nielson KA (2021) A systematic review of cognitive event-related potentials in mild cognitive impairment and Alzheimer's disease. *Behav Brain Res* **396**, 112904.
[53] Rabi R, Vasquez BP, Alain C, Hasher L, Belleville S, Anderson ND (2020) Inhibitory control deficits in individuals with amnestic mild cognitive impairment: A meta-analysis. *Neuropsychol Rev* **30**, 97-125.
[54] Rowe G, Troyer AK, Murphy KJ, Biss R, Hasher L (2021) Implicit processes enhance cognitive abilities in mild cognitive impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, doi: 10.1080/13825585.2021.1998320.
[55] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.
[56] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR (2009) Mild cognitive impairment: Ten years later. *Arch Neurol* **66**, 1447-1455.
[57] Brandt J, Aretouli E, Neijstrom E, Samek J, Manning K, Albert MS, Bandeen-Roche K (2009) Selectivity of executive function deficits in mild cognitive impairment. *Neuropsychology* **23**, 607-618.
[58] Johns EK, Phillips NA, Belleville S, Goupil D, Babins L, Kelner N, Ska B, Gilbert B, Massoud F, de Boysson C, Duncan HD, Chertkow H (2012) The profile of executive functioning in amnestic mild cognitive impairment: Disproportionate deficits in inhibitory control. *J Int Neuropsychol Soc* **18**, 541-555.
[59] Traykov L, Raoux N, Latour F, Gallo L, Hanon O, Baudic S, Bayle C, Wenisch E, Remy P, Rigaud A-S (2007) Executive functions deficit in mild cognitive impairment. *Cogn Behav Neurol* **20**, 219-224.
[60] Cid-Fernández S, Lindín M, Díaz F (2013) Effects of amnestic mild cognitive impairment on N2 and P3 Go/NoGo ERP components. *J Alzheimers Dis* **38**, 295-306.
[61] Cid-Fernández S, Lindín M, Díaz F (2017) Neurocognitive and behavioral indexes for identifying the amnestic subtypes of mild cognitive impairment. *J Alzheimers Dis* **60**, 633-649.
[62] Mudar RA, Chiang H-S, Eroh J, Nguyen LT, Maguire MJ, Spence JS, Kung F, Kraut MA, Hart J (2016) The effects of amnestic mild cognitive impairment on Go/NoGo semantic categorization task performance and event-related potentials. *J Alzheimers Dis* **50**, 577-590.
[63] Nguyen LT, Mudar RA, Chiang H-S, Schneider JM, Maguire MJ, Kraut MA, Hart J (2017) Theta and alpha alterations in amnestic mild cognitive impairment in semantic Go/NoGo tasks. *Front Aging Neurosci* **9**, 160.
[64] López Zunini RA, Knoefel F, Lord C, Breau M, Sweet L, Goubran R, Taler V (2016) P300 amplitude alterations during inhibitory control in persons with mild cognitive impairment. *Brain Res* **1646**, 241-248.
[65] Zhang Y, Han B, Verhaeghen P, Nilsson L-G (2007) Executive functioning in older adults with mild cognitive impairment: MCI has effects on planning, but not on inhibition. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **14**, 557-570.
[66] Borsa VM, Della Rosa PA, Catricalà E, Canini M, Iadanza A, Falini A, Abutalebi J, Iannaccone S (2018) Interference and conflict monitoring in individuals with amnestic mild cognitive impairment: A structural study of the anterior cingulate cortex. *J Neuropsychol* **12**, 23-40.
[67] Luks TL, Oliveira M, Possin KL, Bird A, Miller BL, Weiner MW, Kramer JH (2010) Atrophy in two attention networks is associated with performance on a Flanker task in neurodegenerative disease. *Neuropsychologia* **48**, 165-170.
[68] Thurm F, Antonenko D, Schlee W, Kolassa S, Elbert T, Kolassa I-T (2013) Effects of aging and mild cognitive impairment on electrophysiological correlates of performance monitoring. *J Alzheimers Dis* **35**, 575-587.
[69] Van Dam NT, Sano M, Mitsis EM, Grossman HT, Gu X, Park Y, Hof PR, Fan J (2013) Functional neural correlates of attentional deficits in amnestic mild cognitive impairment. *PLoS One* **8**, e54035.

[70] Wylie SA, Ridderinkhof KR, Eckerle MK, Manning CA (2007) Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia* **45**, 1408-1419.

[71] Zhang Z, Zheng H, Liang K, Wang H, Kong S, Hu J, Wu F, Sun G (2015) Functional degeneration in dorsal and ventral attention systems in amnestic mild cognitive impairment and Alzheimer's disease: An fMRI study. *Neurosci Lett* **585**, 160-165.

[72] Wang P, Zhang X, Liu Y, Liu S, Zhou B, Zhang Z, Yao H, Zhang X, Jiang T (2013) Perceptual and response interference in Alzheimer's disease and mild cognitive impairment. *Clin Neurophysiol* **124**, 2389-2396.

[73] Zurrón M, Lindín M, Cespón J, Cid-Fernández S, Galdo-Álvarez S, Ramos-Goicoa M, Díaz F (2018) Effects of mild cognitive impairment on the event-related brain potential components elicited in executive control tasks. *Front Psychol* **9**, 842.

[74] Rabi R, Chow R, Paracha S, Hasher L, Gardner S, Anderson ND, Alain C (2022) The effects of aging and time of day on inhibitory control: An event-related potential study. *Front Aging Neurosci* **14**, 821043.

[75] Ramos-Goicoa M, Galdo-Álvarez S, Díaz F, Zurrón M (2016) Effect of normal aging and of mild cognitive impairment on event-related potentials to a Stroop Color-Word task. *J Alzheimers Dis* **52**, 1487-1501.

[76] Cespón J, Galdo-Álvarez S, Díaz F (2013) Electrophysiological correlates of amnestic mild cognitive impairment in a Simon task. *PLoS One* **8**, e81506.

[77] Cespón J, Galdo-Álvarez S, Pereiro AX, Díaz F (2014) Differences between mild cognitive impairment subtypes as indicated by event-related potential correlates of cognitive and motor processes in a Simon task. *J Alzheimers Dis* **43**, 631-647.

[78] Cespón J, Galdo-Álvarez S, Díaz F (2015) Inhibition deficit in the spatial tendency of the response in multiple-domain amnestic mild cognitive impairment. An event-related potential study. *Front Aging Neurosci* **7**, 68.

[79] May CP, Hasher L (1998) Synchrony effects in inhibitory control over thought and action. *J Exp Psychol Hum Percept Perform* **24**, 363-379.

[80] May CP, Hasher L, Stoltzfus ER (1993) Optimal time of day and the magnitude of age differences in memory. *Psychol Sci* **4**, 326-330.

[81] Mecacci L, Zani A, Rocchetti G, Lucioli R (1986) The relationships between morningness-eveningness, ageing and personality. *Pers Individ Dif* **7**, 911-913.

[82] Canevelli M, Valletta M, Trebbastoni A, Sarli G, D'Antonio F, Tariciotti L, de Lena C, Bruno G (2016) Sundowning in dementia: Clinical relevance, pathophysiological determinants, and therapeutic approaches. *Front Med* **3**, 73.

[83] Volicer L, Harper DG, Manning BC, Goldstein R, Satlin A (2001) Sundowning and circadian rhythms in Alzheimer's disease. *Am J Pathol* **158**, 704-711.

[84] Naismith SL, Hickie IB, Terpening Z, Rajaratnam SW, Hodges JR, Bolitho S, Rogers NL, Lewis SJG (2013) Circadian misalignment and sleep disruption in mild cognitive impairment. *J Alzheimers Dis* **38**, 857-866.

[85] Ortiz-Tudela E, Martinez-Nicolas A, Díaz-Mardomingo C, García-Herranz S, Pereda-Pérez I, Valencia A, Peraita H, Venero C, Madrid JA, Rol MA (2014) The characterization of biological rhythms in mild cognitive impairment. *Biomed Res Int* **2014**, 524971.

[86] Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju Y-ES (2018) Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol* **75**, 582.

[87] Wilks H, Aschenbrenner AJ, Gordon BA, Balota DA, Fagan AM, Musiek E, Balls-Berry J, Benzinger TLS, Cruchaga C, Morris JC, Hassenstab J (2021) Sharper in the morning: Cognitive time of day effects revealed with high-frequency smartphone testing. *J Clin Exp Neuropsychol* **43**, 825-837.

[88] Welsh KA, Breitner JC, Magruder-Habib KM (1993) Detection of dementia in the elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* **6**, 103-110.

[89] Horne JA, Östberg O (1976) A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* **4**, 97-110.

[90] Adan A (1991) Influence of morningness-eveningness preference in the relationship between body temperature and performance: A diurnal study. *Pers Individ Dif* **12**, 1159-1169.

[91] Roenneberg T, Wirz-Justice A, Merrow M (2003) Life between clocks: Daily temporal patterns of human chronotypes. *J Biol Rhythms* **18**, 80-90.

[92] Sagaspe P, Taillard J, Amiéva H, Beck A, Rascol O, Dartigues J-F, Capelli A, Philip P (2012) Influence of age, circadian and homeostatic processes on inhibitory motor control: A Go/Nogo task study. *PLoS One* **7**, e39410.

[93] Moussard A, Bermudez P, Alain C, Tays W, Moreno S (2016) Life-long music practice and executive control in older adults: An event-related potential study. *Brain Res* **1642**, 146-153.

[94] Picton TW, Bentin S, Berg P, Donchin E, Hillyard S, Johnson R, Miller G, Ritter W, Ruchkin D, Rugg M (2000) Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology* **37**, 127-152.

[95] Berg P, Scherg M (1994) A multiple source approach to the correction of eye artifacts. *Electroencephalogr Clin Neurophysiol* **90**, 229-241.

[96] Zou G (2004) A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* **159**, 702-706.

[97] Cohen J (1988) *Statistical Power Analysis for the Behavioral Sciences*, Routledge, New York.

[98] Anderson JAE, Campbell KL, Amer T, Grady CL, Hasher L (2014) Timing is everything: Age differences in the cognitive control network are modulated by time of day. *Psychol Aging* **29**, 648-657.

[99] Hasher L, Goldstein D, May CP (2005) It's about time: Circadian rhythms, memory, and aging. In *Human learning and memory: Advances in theory and application: The 4th Tsukuba International Conference on Memory*, Izawa C, Ohta N, eds. Lawrence Erlbaum Associates Publishers, pp. 199-217.

[100] Kutas M, Iragui V, Hillyard SA (1994) Effects of aging on event-related brain potentials (ERPs) in a visual detection task. *Electroencephalogr Clin Neurophysiol* **92**, 126-139.

[101] Lorenzo-López L, Amenedo E, Pascual-Marqui RD, Cadaveira F (2008) Neural correlates of age-related visual search decline: A combined ERP and sLORETA study. *Neuroimage* **41**, 511-524.

[102] McEvoy LK, Pellouchoud E, Smith ME, Gevins A (2001) Neurophysiological signals of working memory in normal aging. *Cogn Brain Res* **11**, 363-376.

[103] Polich J (1991) P300 in clinical applications: Meaning, method, and measurement. *Am J EEG Technol* **31**, 201-231.

[104] Saliasi E, Geerligs L, Lorist MM, Maurits NM (2013) The relationship between P3 amplitude and working memory performance differs in young and older adults. *PLoS One* **8**, e63701.

[105] Blasi G, Goldberg TE, Weickert T, Das S, Kohn P, Zoltick B, Bertolino A, Callicott JH, Weinberger DR, Mattay VS (2006) Brain regions underlying response inhibition and interference monitoring and suppression: Brain regions underlying cognitive control. *Eur J Neurosci* **23**, 1658-1664.

[106] Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* **402**, 179-181.

[107] Fassbender C, Murphy K, Foxe JJ, Wylie GR, Javitt DC, Robertson IH, Garavan H (2004) A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. *Cogn Brain Res* **20**, 132-143.

[108] Lie C-H, Specht K, Marshall JC, Fink GR (2006) Using fMRI to decompose the neural processes underlying the Wisconsin Card Sorting Test. *Neuroimage* **30**, 1038-1049.

[109] Monchi O, Petrides M, Petre V, Worsley K, Dagher A (2001) Wisconsin Card Sorting Revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *J Neurosci* **21**, 7733-7741.

[110] Wager TD, Sylvester C-YC, Lacey SC, Nee DE, Franklin M, Jonides J (2005) Common and unique components of response inhibition revealed by fMRI. *Neuroimage* **27**, 323-340.

[111] Liang P, Wang Z, Yang Y, Jia X, Li K (2011) Functional disconnection and compensation in mild cognitive impairment: Evidence from DLPFC connectivity using resting-state fMRI. *PLoS One* **6**, e22153.

[112] Liang P, Li Z, Deshpande G, Wang Z, Hu X, Li K (2014) Altered causal connectivity of resting state brain networks in amnesic MCI. *PLoS One* **9**, e88476.

[113] Chang Y-L, Jacobson MW, Fennema-Notestine C, Hagler DJ, Jennings RG, Dale AM, McEvoy LK, and Alzheimer's Disease Neuroimaging Initiative (2010) Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. *Cereb Cortex* **20**, 1305-1313.

[114] Devanand DP, Mikhno A, Pelton GH, Cuasay K, Pradhaban G, Dileep Kumar JS, Upton N, Lai R, Gunn RN, Libri V, Xinhua Liu, van Heertum R, Mann JJ, Parsey RV (2010) Pittsburgh Compound B (11C-PIB) and Fluorodeoxyglucose (18 F-FDG) PET in patients with Alzheimer disease, mild cognitive impairment, and healthy controls. *J Geriatr Psychiatry Neurol* **23**, 185-198.

[115] Rombouts SARB, Barkhof F, Goekoop R, Stam CJ, Scheltens P (2005) Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI study. *Hum Brain Mapp* **26**, 231-239.

[116] Rosano C, Aizenstein HJ, Cochran JL, Saxton JA, De Kosky ST, Newman AB, Kuller LH, Lopez OL, Carter CS (2005) Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biol Psychiatry* **57**, 761-767.

[117] Borella E, Ludwig C, Dirk J, de Ribaupierre A (2010) The influence of time of testing on interference, working memory, processing speed, and vocabulary: Age differences in adulthood. *Exp Aging Res* **37**, 76-107.

[118] Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ (2013) NIH Toolbox for assessment of neurological and behavioral function. *Neurology* **80**, S2-S6.

[119] Kramer JH, Mungas D, Possin KL, Rankin KP, Boxer AL, Rosen HJ, Bostrom A, Sinha L, Berhel A, Widmeyer M (2014) NIH EXAMINER: Conceptualization and development of an executive function battery. *J Int Neuropsychol Soc* **20**, 11-19.

[120] Morrison GE, Simone CM, Ng NF, Hardy JL (2015) Reliability and validity of the NeuroCognitive Performance Test, a web-based neuropsychological assessment. *Front Psychol* **6**, 1652.

[121] Rabin LA, Spadaccini AT, Brodale DL, Grant KS, Elbulok-Charcape MM, Barr WB (2014) Utilization rates of computerized tests and test batteries among clinical neuropsychologists in the United States and Canada. *Prof Psychol Res Pr* **45**, 368-377.

[122] Belleville S, Gilbert B, Fontaine F, Gagnon L, Ménard É, Gauthier S (2006) Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: Evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord* **22**, 486-499.

[123] Belleville S, Hudon C, Bier N, Brodeur C, Gilbert B, Grenier S, Ouellet M-C, Viscogliosi C, Gauthier S (2018) MEMO+: Efficacy, durability and effect of cognitive training and psychosocial intervention in individuals with mild cognitive impairment. *J Am Geriatr Soc* **66**, 655-663.

[124] Biss RK, Rowe G, Hasher L, Murphy KJ (2020) An incidental learning method to improve face-name memory in older adults with amnestic mild cognitive impairment. *J Int Neuropsychol Soc* **26**, 851-859.

[125] Rapp S, Brenes G, Marsh AP (2002) Memory enhancement training for older adults with mild cognitive impairment: A preliminary study. *Aging Mental Health* **6**, 5-11.

[126] Troyer AK, Murphy KJ, Anderson ND, Moscovitch M, Craik FIM (2008) Changing everyday memory behaviour in amnestic mild cognitive impairment: A randomised controlled trial. *Neuropsychol Rehabil* **18**, 65-88.

[127] Gagnon LG, Belleville S (2012) Training of attentional control in mild cognitive impairment with executive deficits: Results from a double-blind randomised controlled study. *Neuropsychol Rehabil* **22**, 809-835.

[128] Zhao X, Wang L, Ge C, Liu X, Chen M, Zhang C (2020) Effect of process-based multi-task cognitive training program on executive function in older adults with mild cognitive impairment: Study rationale and protocol design for a randomized controlled trial. *Front Psychiatry* **11**, 655.

[129] Hill NTM, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A (2017) Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. *Am J Pathol* **174**, 329-340.

[130] Sherman DS, Mauser J, Nuno M, Sherzai D (2017) The efficacy of cognitive intervention in mild cognitive impairment (MCI): A meta-analysis of outcomes on neuropsychological measures. *Neuropsychol Rev* **27**, 440-484.

[131] Anderson ND, Ebert PL, Grady CL, Jennings JM (2018) Repetition lag training eliminates age-related recollection deficits (and gains are maintained after three months) but does not transfer: Implications for the fractionation of recollection. *Psychol Aging* **33**, 93-108.

[132] Biss RK, Rowe G, Weeks JC, Hasher L, Murphy KJ (2018) Leveraging older adults' susceptibility to distraction to improve memory for face-name associations. *Psychol Aging* **33**, 158-164.

[133] Paradee CV, Rapport LJ, Hanks RA, Levy JA (2005) Circadian preference and cognitive functioning among rehabilitation inpatients. *Clin Neuropsychol* **19**, 55-72.