Sleepiness, parkinsonian features and sustained attention in mild Alzheimer’s disease

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Abstract

Background: we previously demonstrated that patients with mild Alzheimer’s disease and parkinsonian features (AD + PF) are at a higher risk of having daytime sleepiness than mild AD patients without PF (AD – PF).

Objective: to determine whether AD + PF patients demonstrate a known consequence of daytime sleepiness, reduced performance-based sustained attention, compared with AD – PF patients.

Methods: a nocturnal polysomnogram and a next-day multiple sleep latency test (MSLT) were performed. Between MSLT nap opportunities, a 10-min psychomotor vigilance test (PVT) was administered and analysed for reciprocal mean response times (IMEAN), number of lapses (LAPSE) and reciprocal mean slowest 10% (ISLOW).

Results: a total of 35 patients met criteria (AD + PF, n = 16; AD – PF, n = 19). Comparatively, the AD + PF group had slower IMEAN results \( F(1,28) = 6.64, P < 0.05 \) and higher LAPSE rates \( F(1,27) = 7.57, P < 0.05 \). ISLOW measures were not different between groups. When accounting for MSLT results, IMEAN and LAPSE results were no longer significantly different between groups during morning tests, but remained significantly different on afternoon tests.

Conclusion: PFs in mild AD are associated with decreased sustained attention as measured by the PVT. Sleepiness did not fully account for the impairment in sustained attention, suggesting that the presence of PFs has an independent negative association with sustained attention in mild AD.

Keywords: Alzheimer’s disease, parkinsonian features, psychomotor vigilance test, attention, sleepiness, older people

Introduction

Impaired attention is a significant concern in Alzheimer’s disease (AD). In early AD, impaired attention reflects greater pathology in the frontal lobes and associated areas [1], affects driving safety [2, 3] and increases fall potential [4]. Impaired attention is also a core feature of cognitive fluctuation, which impacts activities of daily living and increases caregiver burden [5]. Sleepiness is known to negatively impact attention [6, 7], and a clinical measure of cognitive fluctuation includes the evaluation of sleepiness [8]. However, no studies to date have utilised objective, validated measures of nighttime sleep and daytime sleepiness to determine whether attention is affected in conjunction with or independent from sleepiness in mild AD.

In sleep research, the psychomotor vigilance test (PVT) is considered the gold-standard measure of sustained attention and behavioural alertness [9–11]. The PVT evaluates sustained (or vigilant) attention by measuring response times to visual stimuli that occur at random intervals [9, 12]. Unlike simple reaction time (RT) tests, the PVT generates a large number of responses in a short period of time, allowing for a greater amount of sustained cognitive output without the confounding effects of aptitude or learning [10, 11]. The PVT is highly sensitive to sleep loss [10, 13, 14], causing reliable changes including overall slowing of responses (mean response rate) and increases in errors of omission (lapses) [15]. While laboratory measures of sleep evaluate sleep propensity (i.e. the multiple sleep latency test; MSLT) or wake drive (i.e. maintenance of wakefulness; MWT), PVT results
represent the relative stability (or instability) of sustained attention, reflecting the interaction between sleep-initiating and wake-maintaining systems [10, 11]. PVT results are thus reflective of the two basic responses to sleepiness: the involuntary predisposition to fall asleep and the counteracting drive to sustain alertness [11].

Although sleepiness detrimentally impacts functional capacity in AD [16], the PVT has not been studied in AD. We previously reported that mild AD patients with parkinsonian features (AD + PF) were more likely to have objectively measured, severe daytime sleepiness than mild AD patients without PF (AD – PF). [17] The current analyses were performed to determine whether AD + PF patients have a functional consequence of severe daytime sleepiness, reduced performance-based sustained attention, when compared with AD – PF patients. In subsequent analyses, we examined whether sleepiness moderated the association between PF and sustained attention in AD.

Methods

Patients

The Institutional Review Board approved study protocol, which has been described previously [17]. AD patients with probable AD [18] were recruited for the presence and absence of PF. ‘Mild’ AD was defined by Mini-Mental Status Examination (MMSE) scores ≥20. Exclusion criteria included the following: unstable medical illness (e.g. recent hospitalisation for cardiac disease); use of dopaminergic medications, which may affect PF and/or sleepiness; use of sedating/stimulating medications, which may affect nocturnal sleep and/or sleepiness; symptoms of moderate–severe depression within the past month, defined by a Geriatric Depression Scale score ≥19 [19]. Medications for depression and cognition were allowed if doses remained stable and were taken for greater than 3-months prior to study.

Study protocol

Telephone screen

Patients were ineligible if they reported highly variable sleep/wake routines or had common symptoms of sleep disorders, including sleep apnoea (e.g. snoring) or parasomnias (e.g. dream enactment). If eligible, patients completed 2–4 weeks of sleep diaries to record habitual bedtimes and wake times (confirmed by caregiver) prior to the overnight sleep study (PSG) and next-day MSLT. Of the 62 patients meeting study criteria, 36 AD patients and their caregivers provided consent (58% response rate).

Assessment of parkinsonian features

PFs were evaluated using the modified motor Unified Parkinson’s Disease Rating Scale (mmUPDRS) [20]. Four domain scores were rated (bradykinesia; gait disturbance; rigidity; tremor) and summed for a total mmUPDRS score (protocol maximum = 100). Unlike Parkinson’s disease, AD patients have low mmUPDRS scores [21] and were therefore grouped by the absence (mmUPDRS score of zero) or the presence (non-zero mmUPDRS score) of PF.

PSG/MSLT

PSG bedtime and wake time were scheduled according to the sleep diary [17]. The next-day MSLT started 2-h after morning wake time and every 2-h thereafter, for a total of 4-naps. Sleep-onset was defined as the first epoch of any stage of sleep. Naps were terminated 15-min after sleep-onset to allow for possible sleep-onset REM periods, or after 20-min if no sleep occurred. The mean sleep latency (‘mean MSLT’) was calculated as the average value over four-naps. The mean MSLT ranges from 0 to 20 min, with lower scores reflecting higher propensity for sleepiness. Clinically, mean MSLT scores <10.4 min are considered indicative of sleepiness [22].

Neurobehavioural measures

Several studies have utilised neurocognitive assessment via brief computerised tests [9, 11, 23]. A practice session was administered 1-h before bedtime of the PSG. For data collection, the computerised battery was administered four-times during the following day, 1-h before each MSLT nap. The computerised protocol included: a 10-min PVT; a 4-min addition/calculation test (ADD); a 2-min digit symbol substitution test (DSST) and a probed recall memory (PRM) test, which is a short-term memory task [24].

During the PVT, a blank box appeared in the middle of the computer screen which randomly started as a millisecond counter. Patients were instructed to press a button with the thumb of their self-identified dominant hand to stop the counter as quickly as possible. The interstimulus interval varied randomly between 2 and 10 s. Response times greater than 100 ms were regarded as valid. Responses less than 100 ms were considered false starts (including pushing the button without a stimulus). Responses greater than 500 ms were considered errors of omission (LAPSE). If the button was not pushed after 10 s, a telephone sound alerted the patient to the task. If the button was not released after 3 s, the response was considered an error and excluded from analyses.

The ADD and DSST are tests of cognitive speed and were used to complement the PVT. During practice sessions, patients (regardless of PF group) exhibited difficulty using the computer keyboard, adversely affecting response times for the ADD, DSST and PRM. As the goal of these tests was to measure cognitive speed, the protocol was adjusted so that patients verbally responded to these test cues, which were subsequently typed in by research personnel.
**Statistical analysis**

Statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS, Inc., 2006, Chicago, IL, USA). Baseline characteristics between groups were examined using t-tests. Data from the neurobehavioural measures were analysed for each daytime test (tests 1, 2, 3 and 4). The largest effect sizes occur with the reciprocal (or inverse) of the mean response times (IMEAN), the reciprocal (or inverse) of the mean of the slowest 10% response times (ISLOW) and the number of lapses (errors of omission, ‘LAPSE’) [25]. For IMEAN and ISLOW, reciprocal response times have less vulnerability to extremely slow response times, yielding a more normal distribution than actual response times and allowing for emphasis on changes of optimal and intermediate responses, even if small changes are detected [25]. Thus, IMEAN, LAPSE and ISLOW measures were analysed.

Given the multiple time points (tests 1, 2, 3 and 4), data were first analysed using mixed between-within subjects ANOVAs to determine whether an interaction effect was present and whether main effects were present by time or by group. If main effects were found, t-tests were used to compare group means at specific time points. A subsequent analysis was then performed to evaluate the potential role of nocturnal total sleep time (TST) and daytime sleepiness, using mixed between-within subjects ANCOVAs with TST from the PSG and mean MSLT as covariates. A priori significance was $P < 0.05$.

**Results**

**Baseline characteristics**

A total of 35 patients ($\text{AD} - \text{PF} = 19$, $\text{AD} + \text{PF} = 16$) completed the PSG, MSLT and neurobehavioural measures. In the $\text{AD} - \text{PF}$ group, computer error caused missing data for one patient and missing data on tests 1 and 2 for another patient. In the $\text{AD} + \text{PF}$ group, one patient chose to stop the computer tests after test 2. Because the nature of statistical methods allowed for time point analyses, data were analysed inclusively.

Patient characteristics are presented in Table 1. Four patients had sleep apnoea (apnoea–hypopnoea index >15), but only one had a mean MSLT $<10.4\text{ min}$ [22]. All patients reported taking a cholinesterase inhibitor, either alone or in combination with memantine. Other sleep data were reported previously [17].

**Neurobehavioural test results for AD + PF and AD − PF groups**

No significant interaction effects were found on any neurobehavioural test measure. Main effects were analysed for group differences by time (test session) or group (presence/absence of PF).

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**PVT**

Figure 1 represents the mean scores for IMEAN, LAPSE and ISLOW. There were no significant main effects for time. For IMEAN and LAPSE, a main effect was found for PF group. The $\text{AD} + \text{PF}$ group had slower IMEAN and more LAPSE on tests 1, 2, 3 and 4. (Table 2) For ISLOW, there was a borderline significant main effect for PF group [$F_{(1,28)} = 4.18$, $P = 0.050$], with $\text{AD} + \text{PF}$ patients performing more slowly on test 3 compared with $\text{AD} − \text{PF}$ patients [$F_{(1,32)} = 7.08$, $P = 0.01$].

**Other measures**

The ADD was evaluated for number of attempts and number correct. The DSST was evaluated for the number of correct responses. No significant differences were found between groups on either measure. All patients scored zero on the PRM test.

**Assessment of sleepiness and PVT results**

With TST and mean MSLT as covariates, no interaction effect was found for IMEAN. The main effect of time remained non-significant. The main effect of PF group remained significant. Group differences remained significant on tests 3 and 4 but were no longer significant on test 1 ($P = 0.10$) and test 2 ($P = 0.09$), suggesting that sleepiness accounted for group differences during the morning test sessions (Table 2).

With TST and mean MSLT as covariates, no interaction effect was found for LAPSE. A main effect for time emerged (Wilks’ lambda $= 0.72$, $P = 0.049$). The main
effect of PF group remained significant. Group differences on tests 3 and 4 remained significant but were no longer significant on test 1 \((P = 0.08)\) and test 2 \((P = 0.07)\) (Table 2).

**Discussion**

We utilised the PVT, a reliable and validated measure of sustained attention, in mild AD patients to determine whether sustained attention is impacted by the presence of PFs, and if so, whether this association was accounted for by daytime sleepiness [17]. Our results demonstrate that mild AD patients with PF are generally slower in response times (IMEAN) and have more errors of omission (LAPSE) than mild AD patients without PF. Performance on other neurobehavioural measures was not different between these groups, suggesting that sustained attention was specifically impacted. Further, sleepiness only partially accounted for the differences in sustained attention between groups. Together, these results suggest that PFs have a negative association with sustained attention in mild AD, independent of sleepiness.

Studies evaluating RTs in dementia report variable findings when PF are present. One study demonstrated slower and more variable RTs in dementia patients with PF [26], while another demonstrated variable but not slower RTs in dementia patients with PF [27]. This discrepancy may be partially due to differences in the utilisation of simple RT tests, which are generally criticised for lack of validation and reliability [28]. A strength of our study is the use of the PVT, which has high test–retest reliability and is a validated measure of sustained attention [9–11].

Our AD + PF patients were slower on average and had more variability. As PFs may generally impair RTs, it is possible that the motor features of the AD + PF group contributed to their slower IMEAN results. However, motor issues should have also affected ISLOW results, which were not significantly different between AD − PF and AD + PF groups. Similarly, praxis difficulties may accompany PF, but
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praxis issues should have also affected the fastest 10% response times (data not shown) which were also not significantly different between groups. Lower MMSE scores may correlate with RTs [26], so it is possible that the slightly lower MMSE scores of our AD + PF group was a factor in the PVT results. However, we speculate that this difference should have also affected other neurobehavioural test measures of shorter duration (DSST, ADD), which were not different between groups and were consistent within each group. Together, these results suggest that rather than motor or cognitive speed, sustained attention was affected by the presence of PFs in these mild AD patients.

Sleepiness is associated with a decline in sustained attention [16] and significantly contributes to cognitive fluctuation [8]. One concern in grouping attention and sleepiness in a single clinical evaluative tool is the inability to evaluate the contribution of nighttime sleep disturbance to daytime sleepiness. A strength of the current study is the use of objective measures of nocturnal sleep (PSG) and daytime sleepiness (MSLT). We previously demonstrated that the AD + PF group was significantly sleepier than the AD−PF group, despite relatively preserved nighttime sleep [17].

In the current analyses, we used the prior night’s TST and MSLT results to determine whether differences in PVT results between groups were reflective of states of sleep and sleepiness.

We found that sleepiness explained some but not all of the association between PF and sustained attention in our mild AD patients. Sleepiness accounted for PVT differences between groups in the morning, when wake drive should be maximal. As PF in AD are associated with pathological involvement in areas of the brain not yet clearly identified, it is possible that a relatively impaired circadian system [29, 30] manifests as a blunted morning wake drive in our AD + PF patients. The PVT reflects the balance between sleep and wake drives, and we chose to use the MSLT to evaluate sleepiness rather than the MWT to evaluate wake drive. Further analyses on nighttime sleep would be helpful in evaluating whether microarchitecture differences in nighttime sleep contribute to these differences in the morning.

The use of reliable and validated measures of sleep, sleepiness and sustained attention are strengths of the study. The current study also has limitations. Because of our small sample size (n = 35), analyses were limited to detecting large effect sizes. With a larger sample size, small and medium effects may have been detected. Additionally, the small and selected nature of the cohort limits the ability to generalise to the AD population. While our groups were selectively matched for important factors including age, sex and BMI, other potential confounding variables such as use of caffeine, alcohol and nicotine were not taken into consideration. Definitive confirmation of disease state (i.e. autopsy) was not possible, so our AD + PF patients may have included patients with Lewy body dementia. Finally, although the PVT is very sensitive for sleep and wake instability [10, 13, 14], it is unknown whether the PVT is the most valid test of sustained attention in older adults and in AD specifically. We compared PVT results taking into account daytime sleepiness, but future studies may want to evaluate PVT results to more a traditional measure of alertness, such as the MWT, in this population.

In summary, the present analyses demonstrate that PFs in mild AD are associated with impaired sustained attention that is not fully explained by the presence of sleepiness. Longitudinal research is needed to investigate the association between cognition, PFs, sleepiness and alertness in AD. Neuropathology studies may also help in deciphering the clinical association of PFs with impaired sustained attention in early AD.

Key points

- In sleep research, the PVT is considered the gold-standard test of sustained attention.
- We previously demonstrated that PFs in mild AD patients are associated with severe daytime sleepiness.
- In this study, the PVT was administered to determine whether PF in mild AD was associated with decreases in sustained attention.
- We also evaluated whether sleepiness, which affects PVT results, modified the association between PF and sustained attention.
- The presence of PFs in mild AD is associated with decreased sustained attention, independent of sleepiness.

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References


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