Time of day and caffeine influence some neuropsychological tests in the elderly

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Abstract

We report that performance on neuropsychological tests used in the diagnosis of dementia can be influenced by external factors such as time of day (TOD) and caffeine. This study investigates TOD effects on cognitive performance in the elderly. The optimal TOD at which an individual is at their maximal arousal alters with age and in the elderly typically occurs in the morning. Neuropsychological test scores from healthy elderly participants were analysed to determine whether TOD affected performance. Interactions between caffeine and TOD were also investigated. Across two data sets that were analysed, significant TOD effects were noted for Pattern Comparison Speed (PCS), Letter Comparison Speed (LCS), Trail Making Test Part A, Mini Mental State Examination (MMSE) and the Graded Naming Test (GNT), revealing a decline in test scores as TOD increases. Significant interactions between TOD, age and the PCS, LCS and Trail Making part A were noted in data set one. In data set two, where caffeine intake had been controlled for, significant interactions between caffeine, TOD and scores on the MMSE and GNT were found. The TOD and caffeine effects highlight the need to control for these external factors when scoring the assessments. This conclusion has implications for the clinical procedure of diagnosis and treatment of dementia and Alzheimer's.

Key Words: Time of Day, Caffeine, Neuropsychological testing, Aging, Alzheimer's disease.

Introduction

Neuropsychological testing forms a part of the diagnostic process for the detection of dementia and mild cognitive impairment (MCI) (Overshott & Burns, 2004). Many of the assessments are influenced by external factors, which if not controlled or considered, may complicate clinical inferences derivable from the tests (Overshott & Burns, 2004; Jacova, Kertesz, Blair, Fisk, & Feldman, 2007; Forlenza, Diniz, & Gattaz, 2010; Ashford et al., 2006). Such factors can include mood (Jacova et al., 2007), presence of caffeine (Lesk, Honey, & de Jager, 2009) and time of day (TOD) (Schmidt, Collette, Cajochen, & Peigneux, 2007). In this work we focus on TOD and caffeine and their interaction.

Time of day

Circadian peak efficiency, the TOD that at which individuals are at their optimal arousal, alters during aging (Hasher, Goldstein, & May, 2005). As a result, 75% of older individuals subjectively report that they are 'morning types' in comparison to only 7% of younger adults (Yoon, May, & Hasher, 1999). The preference for 'morningness' has implications for cognitive performance. Young adults show improvements in performance during the day with peak efficiency in the afternoon whereas the elderly experience a deterioration in performance in the afternoon and evening (Yoon et al., 1999).

Hasher, Zacks, and Rahhal (1999) reported that when the individual chooses the time at which to take an assessment their performance is optimised. As a result age-related deficits are more marked when older participants are tested at their non-optimal time (Intons-Peterson Rocchi, West, McLellan, & Hackney, 1999). Under normal sleep-wake patterns the young

outperform the old in most cognitive domains, although this is not as pronounced when the assessment takes place at the chosen optimal time for each sub-group (Winocur & Hasher, 2004). This effect has been noted on assessments of word span (Yoon et al., 1999), sentence recognition (May, Hasher, & Stolzfus, 1993), cued recall (May, Hasher, & Foong, 2005) and story recall (Winocur & Hasher, 2004). A similar effect is seen in assessments of executive function (EF). Whilst younger adults generally outperform older adults at inhibitory tasks (Zacks & Hasher, 1994), age differences are reduced when older adults are tested at their preferred TOD, i.e. the morning. Studies which do not consider the time that participants are tested may report exaggerated differences, potentially degrading the significance of the results obtained, and possibly biasing the clinical diagnosis of cognitive deficits.

TOD effects on cognitive performance in the elderly do not affect all cognitive processes equally. Tasks assessing EF seem to be especially vulnerable, with significant TOD effects reported for tasks engaging attentional and inhibitory processes (Hasher, Lustig, & Zacks, 2007; Yang, Hasher, & Wilson, 2007). The investigation of TOD effects on other cognitive domains has not been widely investigated, however, TOD does not appear to affect tasks which utilise well-established knowledge such as sentence completion or vocabulary (Borella, Ludwig, Dirk, & Ribaupierre, 2011). Tasks longer in duration with a high cognitive load are more likely to be affected by TOD (Schmidt et al., 2007). It is, thus, clear that the characteristics of the task employed affects the degree of vulnerability to TOD effects.

Previous research on the elderly has demonstrated that the prior consumption of caffeine can affect neuropsychological test performance (Lesk et al., 2009). Lesk, Honey, and de Jager (2009) investigated the effects of caffeine-containing foodstuffs (CCFS) on cognitive performance in a group of elderly participants and found that in those who had consumed CCFS up to four hours prior to testing there were significant interaction effects between age and tests of processing speed, semantic memory, visuospatial associative

memory and EFs. This interaction was not seen for participants who had not consumed CCFS prior to testing. These results highlight the need to consider prior caffeine consumption when scoring neuropsychological tests and when comparing results to normative data. As CCFS are commonly consumed it is important to investigate whether 200mg of pure caffeine, which is equivalent to one strong cup of coffee, can further interact with the TOD that tests are administered on test scores.

The present study

There is minimal literature investigating TOD effects across all cognitive domains or on assessments commonly used at the primary consultation such as the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The MMSE is currently recommended by the National Institute for Health and Care Excellence (NICE) as one of the brief cognitive assessments to be used in the diagnosis of dementia. Further, the score obtained on this assessment can be considered to determine whether or not a patient is prescribed medication (National Institute for Health and Care Excellence [NICE], 2011). It is therefore important to understand any problems that might contribute to the unreliability of the use of these tests in clinical diagnosis.

Here we report our investigations of TOD effects on two data sets from our studies in which we administered a battery of assessments testing a variety of cognitive domains. One of the data sets is from a study that investigated prior intake of caffeine on neuropsychological testing (Lesk and Walters, 2012). Taken together, we can analyse and report on the effects of TOD and of 200mg of pure caffeine, and on their interactions on the neuropsychological assessments administered.

Methods

Participants

Participants for both studies were recruited from the over-60s participant pool at the Division of Psychology, University of Bradford which comprises a cross-section of members of the local Bradford community who were recruited into the pool from a number of outreach events. All participants gave their full informed written consent to take part. All participants were cognitively healthy.

Two data sets of neuropsychological assessment scores were reviewed. Data set one arose in an investigation of the relationship between fish intake and cognitive function in the elderly (unpublished). The inclusion criteria specified that participants must be at least 60 years of age and be cognitively healthy with no existing diagnosis of any neurological disease or memory impairment. The mean age of the participants (n=36) was 72.53 (±6.09) years. Data set two is derived from an investigation of the effect of prior caffeine consumption on cognitive performance (Lesk and Walters, 2012). The analysis and conclusions reported here depend on both data sets. All participants completed the full battery of neuropsychological tests in the same order.

For data set two which investigated the effect of prior caffeine consumption on cognitive performance, the inclusion criteria specified that participants must be 60 years of age or older, be neurologically and cognitively healthy, be regular caffeine consumers and must not have been advised by their doctor to avoid caffeine consumption. The exclusion criteria specified that smokers were not able to take part due to the effects of nicotine on the half-life of caffeine. Likewise, participants who consumed excessive amounts of caffeine, i.e.

>400mg per day, were not permitted to take part. The mean age of participants (n=40) was 73.35 (±6.56) years. Participants had abstained from caffeine for 12 hours prior to testing and alcohol for 24 hours prior to testing and were randomly divided into two groups (a between-subjects factor). One group received 200mg of caffeine prior to the neuropsychological assessment (n=20) and the second group received a placebo (n = 20).

Materials

A neuropsychological assessment battery used to assess cognitive performance consisted of the following tests:

MMSE - the MMSE is a test of general cognitive function assessing a variety of cognitive domains (Folstein, Folstein, & McHugh, 1975). Participants receive a score out of 30.

MoCA - the MoCA is a quick test of general cognitive performance (Nasreddine et al., 2005). Participants receive a score out of thirty and are given an extra point if they have less than 12 years education.

Word Recall - this is an assessment of short-term memory and requires the participant to recall as many words as possible from a list of 15 common nouns read aloud by the researcher. This test was created by the researcher using the MRC Psycholinguistics database and the words were controlled for word length, frequency and imaginability (Coltheart, 1981).

CANTAB Paired Associate Learning (PAL) - this is an assessment of visuo-spatial associative memory (Sahakian et al., 1988) and requires the participant to learn an association between a visual stimulus and a spatial location (Egerházi, Berecz, Bartöok, & Degrell,

2007). The test is delivered via a touch screen and the number of errors at the six-pattern stage is of importance.

CANTAB Graded Naming Test (GNT) - this is an assessment of semantic memory (McKenna & Warrington, 1980) and requires the participant to name 30 displayed objects.

Symbol Digit Modalities Task (SDMT) - this test is an assessment of EF and requires the participant to complete a grid using a key of symbols and corresponding numbers (Smith, 1968). The participant is given 90 seconds to work through the grid using the key and writing the correct number underneath each corresponding symbol. The number of errors and the total number of correctly matched symbol number pairs are recorded.

Stroop Test - this test assesses both EF and processing speed. The Stroop consists of a list of colour words which are all presented in an incongruent colour (Trenerry, Crosson, DeBoe, & Leber, 1989). Participants are given 30 seconds to read down each column of words first stating the word as the text appears. Secondly they are timed for 30 seconds and are required to read the colour of the ink the word is presented in. This same method of administration was used in Lesk et al. (2009) to allow direct comparisons between the two studies.

Pattern Comparison Speed (PCS) and Letter Comparison Speed (LCS) - both of these tests assess processing speed (Salthouse & Babcock, 1991). Participants are asked to state whether two patterns or strings of letters are the same or different. They are timed for 20 seconds and are required to complete as many pairs as possible. This same method was used in Lesk et al. (2009) to allow direct comparisons between the two studies.

Digit Span and Digit Score - digit span assesses working memory (Wechsler, 1981). A series of numbers is read aloud to the participant starting with a sequence length of three

numbers, increasing to a sequence of nine. The test ends when the subject is unable to recall two sets of a certain length. The digit span score is the number of digits in this last successful set. Digit Score is the total number of strings correctly repeated.

Dual Tasks (DT) - this is a test of EF which participants are given a page depicting a string of boxes and are timed for one minute to put a cross in each box following the direction of the string (Baddeley, Della Sala, Papagno, & Spinnler, 1997). Participants then repeat the task but are simultaneously required to remember strings of numbers (based on their digit span score; see above). Scores used are the difference in the number of boxes crossed between the first and second times (DT T1- T2) and the dual task ratio (DTR) which is calculated as the ratio of boxes crossed to the number of digit strings remembered.

Trail Making Test - this two part test assesses visual attention and EF (Reitan, 1958). Part A, an assessment of visual attention, requires participants correctly to join up a series of circles, each of which contain a number, in ascending numerical order as quickly as they can. Part B, an assessment of EF, specifically flexibility (May & Hasher, 1998), requires participants to join up a series of circles containing either a letter or a number, alternating between ascending numerical order and ascending alphabetical order. Participants are timed and must complete the task as quickly as possible.

Results

Data sets from two studies by the researchers were analysed for TOD effects. TOD was not controlled for. The aim of the current study was to investigate whether the TOD at which tests are administered can influence the score obtained on neuropsychological

assessments, and whether caffeine consumption interacts with TOD effects on cognitive test scores.

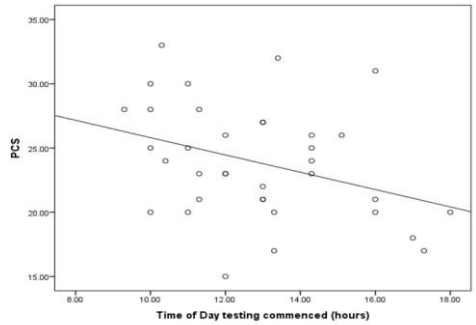
Analysis of data set one for main effects of time of day on cognitive test scores

The mean scores for each neuropsychological test for participants tested in the morning (AM) and afternoon (PM) can be seen in table one.

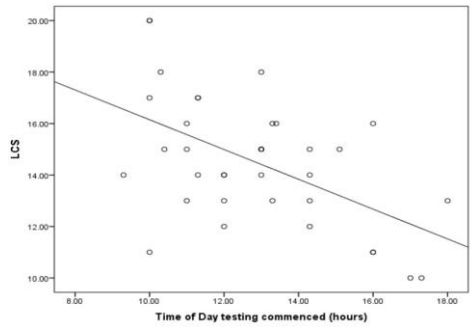
Table 1: Data set one, mean neuropsychological test scores for participants tested in the morning (AM) and afternoon (PM)

Test	**AM (mean ±*S.D*)**	**PM (mean ± *S.D*)**
MoCA	28.08 (±1.32)	27.30 (±2.20)
MMSE	28.54 (±1.56)	28.61 (±1.62)
Digit Span	7.08 (±1.12)	6.78 (±1.04)
DTR	1.02 (±0.05)	0.96 (±0.25)
Stroop Word	64.92 (±6.53)	59.87 (±13.51)
Stroop Interference	27.85 (±6.52)	25.43 (±5.22)
PCS	25.77 (±4.13)	22.83 (±4.31)
LCS	15.92 (±2.63)	13.70 (± 2.05)
Trail Making A	29.00 (±10.47)	38.26 (±13.72)
Trail Making B	60.62 (±16.57)	74.87 (±22.32)

A multivariate analysis of covariance (MANCOVA) with test scores entered as the dependent variables and TOD entered as a covariate was used. Significant main effects of TOD were present for the PCS [$F(1,33) = 4.72$, $p<0.05$], LCS [$F(1,33) = 13.51$, $p<0.01$] and part A of the Trail Making test [$F(1,33) = 4.29$, $p<0.05$]. Regression analysis revealed a linear decrease in performance for all these assessments as TOD progresses [PCS, [$\beta = -0.35$, ($F(1,34) = 4.77$, $p <0.05$), y-axis intercept = 32.55 with regression correlation coefficient $r = 0.35$, $p <0.05$], LCS, [$\beta = -0.54$, ($F(1,34) = 13.67$, $p <0.01$), y-axis intercept = 21.94 with regression correlation coefficient $r = 0.54$, $p <0.01$] and Trail Making part A, [$\beta = 0.33$, ($F(1,34) = 4.23$, $p <0.05$), y-axis intercept = 10.28 with regression correlation coefficient $r = 0.33$, $p <0.05$]. Scatter plots of these results can be seen in figure one. For no other tests were TOD effects found to be significant.



(A)



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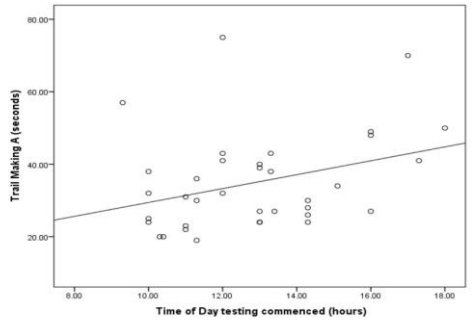

(C)

Figure 1: A linear decrease in performance is seen as time spans into the afternoon on assessments of (A) PCS, (B) LCS and (C) Trail Making part A. A positive correlation is presented in the Trail Making test part A signifying that as TOD progresses participants take longer to complete the task. The TOD variable on the x axis is plotted in 24 hour clock format whereby 0-12 represents the morning hours and 13.00 hours onwards represents the afternoon.

Analysis of data set two for main effects of time of day on cognitive test scores

The mean scores for each neuropsychological test for participants tested in the morning (AM) and afternoon (PM) can be seen in table two.

Table 2: data set two, mean neuropsychological test scores for participants tested in the morning (AM) and afternoon (PM)

Test	**AM (mean ±*S.D*)**	**PM (mean ± *S.D*)**
MMSE	28.89 (±1.15)	28.29 (±0.96)
SDMT total	40.84 (±7.38)	40.86 (±7.69)
SDMT T-E	39.95 (±7.37)	38.90 (±9.04)
Stroop Word	52.63 (±20.62)	52.10 (±12.40)
Stroop Interference	27.68 (±7.34)	28.14 (±12.29)
Word Recall	5.21 (±1.65)	4.95 (±1.60)
PCS	24.11 (±4.41)	23.62 (±4.93)
LCS	13.63 (±3.61)	14.47 (±3.54)
PAL 6 pattern errors	8.00 (±7.12)	7.29 (±5.96)
GNT	27.21 (2.30)	24.86 (2.78)
Digit Span	6.58 (1.02)	6.19 (0.75)
Digit Score	9.11 (1.91)	8.48 (1.50)
DTR	0.96(0.15)	0.96 (0.20)

To explore TOD effects on neuropsychological performance all cognitive tests were submitted to a MANCOVA with test scores entered as the dependent variables and TOD as a covariate. There were significant main effects of TOD on the MMSE [F (1, 38) = 9.01, $p<0.01$] and the GNT [F (1, 38) = 7.69, $p<0.01$]. TOD was a significant predictor of MMSE score [$\beta = -0.24$, F (1, 38) = 9.01, $p < 0.01$ y-axis intercept – 31.55, with regression coefficient $r = 0.44$ $p < 0.01$] and GNT score [$\beta = -0.58$, F (1, 38) = 7.69, $p < 0.01$) y-axis intercept = 33.18, with regression coefficient $r = 0.41$, $p < 0.01$] revealing a linear decrease in test score as TOD increases for both tests. See figure two for scatter plots. For no other tests were TOD effects found to be significant.

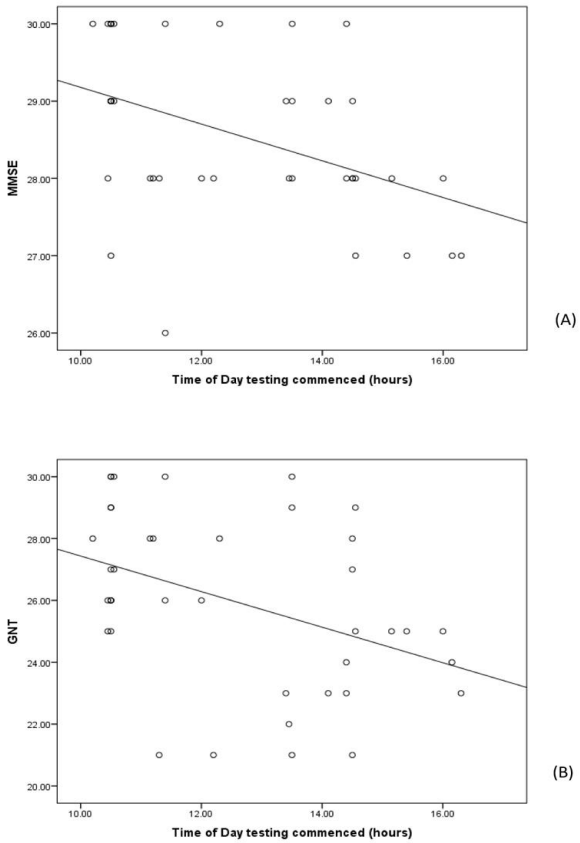

Figure 2: A linear decrease in performance is seen as TOD spans into the afternoon for (A), the MMSE and (B), the GNT. The TOD variable on the x axis is plotted in 24 hour clock format whereby 0-12 represents the morning hours and 13.00 hours onwards represents the afternoon.

Analysis of data set two for interaction effects of time of day and caffeine

Using Levene's test, homogeneity of variances were equal for all neuropsychological test scores between the caffeine and placebo conditions ($p>0.05$). To investigate the effect of caffeine on the tests administered in data set two all tests were submitted to a multivariate analysis of variance (MANOVA) with the test scores entered as the dependent variables and drug group (caffeine/placebo) as a fixed factor. There was no significant difference between the caffeine or placebo group on any of the assessments used.

To assess prior caffeine consumption and any interaction with TOD all cognitive tests were submitted to a MANCOVA with drug group (caffeine or placebo) entered as a fixed factor and TOD as a covariate. An interaction term was included in the model. Significant interactions between drug group, TOD and both MMSE [F (2, 37) = 4·78, $p<0·05$] and GNT [F (2, 37) = 3·96, $p < 0·05$] score were found. See figure three for scatter plots of these interactions.

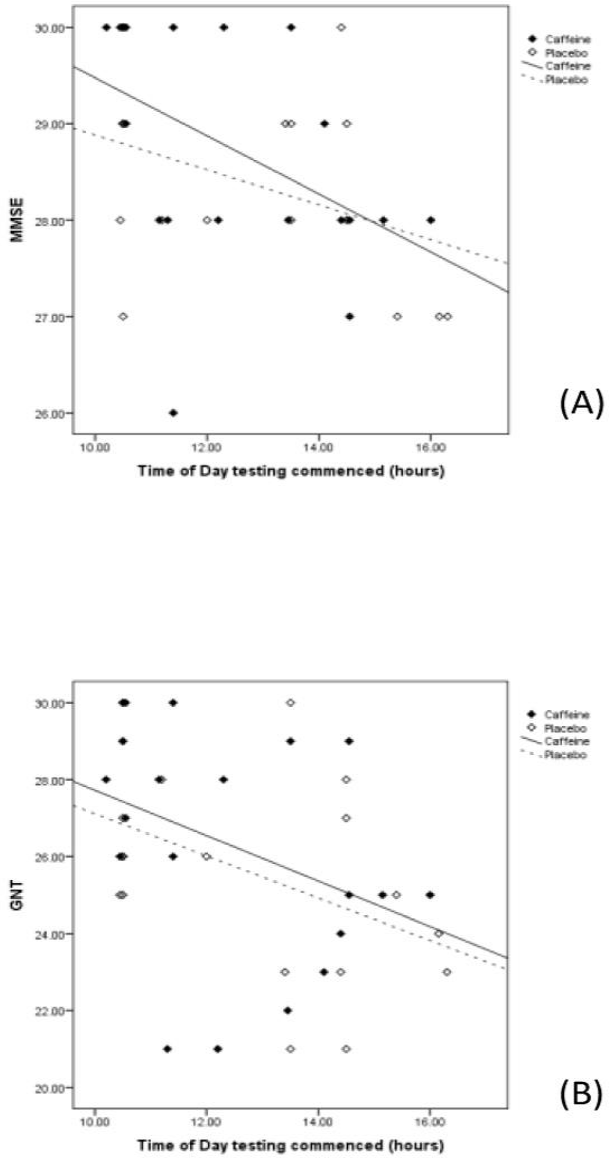

Figure 3: Interactions between caffeine x TOD and scores for (A) the MMSE and (B) the GNT. There is a significant linear decrease in performance as time spans into the afternoon. The TOD variable on the x axis is plotted in 24 hour clock format whereby 0-12 represents the morning hours and 13.00 hours onwards represents the afternoon.

Analysis of interaction effects of age x time of day x test scores

Given the age x CCFS interaction effect of Lesk et al. (2009) and Drug group x Age interaction effect of Lesk and Walters (2012) we now seek to investigate any interaction effects of TOD and age (data set 1) and any possible three-way interactions of caffeine, age and TOD (data set 2).

Data Set One: In order to examine interactions between age and TOD on neuropsychological test scores all tests were submitted to a MANCOVA with age and TOD entered into the model as covariates and tests scores entered as dependent variables. Significant interactions with age, TOD and scores on the PCS [F (1, 33) = 8.22, p <0.01)], LCS [F (1, 33) = 18.79, p <0.001] and Trail Making part A [F (1, 33) = 9.05, p< 0.01] were found. For all of these tests the older elderly perform worse than the younger elderly as TOD increases. No other tests were found to be significant.

Data Set Two: In order to examine interactions between caffeine/placebo, age and TOD on neuropsychological test scores all tests were submitted to a MANCOVA with caffeine/placebo as a fixed factor, age and TOD as covariates and test scores as dependent variables. Three separate interactions were included in the model.

Significant three-way interactions between drug group, age and TOD were found on the MMSE [F(2,37)= 5.26, p <0.05], SDMT total responses [F(2,37)= 3.92, p <0.05)], SDMT T-E [F(2,37)= 3.90, p <0.05], LCS [F(2,37)= 3.42, p <0.05), and GNT [F(2,37)= 5.43, p < 0.01]. The older elderly who received caffeine perform significantly worse than the younger elderly as TOD increases throughout both the morning and the afternoon. No other tests were found to be significant.

Discussion

In this study we have investigated (1) the influence of TOD and (2) the interaction of caffeine with TOD on the performance of elderly participants on a series of neuropsychological assessments.

Analysis of data set one showed a significant effect of TOD on two assessments of processing speed, the PCS and LCS, and on one assessment of visual attention, Trail Making part A. Analysis of data set two showed a significant effect of TOD for one assessment of general cognitive function, the MMSE, and one test of semantic memory, the GNT. All of these assessments over both data sets show a decrease in performance as TOD spanned into the afternoon.

In data set one significant interactions between age, TOD and scores on the PCS, LCS and Trail Making part A were noted. Significant interactions between caffeine, TOD and score were found for the MMSE and GNT in data set two. Significant three way interactions between TOD, age and drug group were present for the MMSE, SDMT total, SDMT T-E, LCS and GNT in data set two, revealing the older elderly who received caffeine performed significantly worse as time advanced through the day compared to the younger elderly. The older elderly who received placebo did not show as significant a decline in performance.

In the present paper, for data set two, a significant effect of TOD was noted on the GNT, whereby, participants who completed the assessment in the afternoon scored lower than those completing the test in the morning. Previous research has failed to find significant effects of TOD on assessments of semantic knowledge (May & Hasher, 1998). Therefore this report contains novel observations.

The GNT has previously been shown to be highly sensitive to the detection of mild degrees of cognitive impairment and early AD (Blackwell et al., 2004). Blackwell et al. (2004) demonstrate in a regression analysis that the number of errors made at the six pattern stage of the CANTAB PAL, the score obtained on the GNT and the subject's age at the time of testing, can identify converters to AD with 100% accuracy within a 32 month period using a sample of 40 patients. The significant effect of TOD on GNT score in the present study demonstrates that caution should be applied when using such algorithms which may not have considered additional external factors such as TOD.

Furthermore, data set one in the present study found significant TOD effects for two assessments of processing speed, the PCS and LCS. A linear decrease in performance was noted for both assessments as TOD spanned into the afternoon. Processing speed relies on attention mechanisms and frontal functioning, therefore, it would be expected that this domain would be susceptible to tiredness and TOD effects. To our knowledge no other studies have specifically investigated the effects of TOD on this cognitive domain in the elderly.

Previous literature investigating TOD effects in the elderly has noted significance for tasks of EF whereby the elderly perform significantly worse on these tasks in the afternoon (Zacks & Hasher, 1994; Hasher et al., 2007). This has been found mostly for EF tasks with an inhibitory component (Hasher et al., 2007; Yang et al., 2007). EF relies heavily on the frontal lobes which are known to be highly vulnerable to the aging process, with marked changes in physiology and anatomy of these areas in the elderly (Bugg, DeLosh, & Clegg, 2006). Intons-Peterson, Rocchi, West, McLellan, & Hackney, (1998) and West, Murphy, Armilio, Craik, and Stuss (2002) also reported TOD effects on inhibitory tasks in the elderly. The present study failed to find TOD effects on three assessments of EF the SDMT, Stroop Interference and the DT.

Caffeine and time of day

The second aim of the present study was to investigate whether caffeine, a commonly consumed stimulant (Nawrot et al., 2003), interacted with the TOD that assessments were delivered to affect test scores. Significant interactions between TOD, caffeine and score on the MMSE and GNT were found. Those participants who had consumed 200mg of pure caffeine 40 minutes prior to the completion of the MMSE in the morning performed better than those who received placebo. In the afternoon a linear decrease in performance was observed for both subgroups, however, those participants who received caffeine performed worse as time spanned further into the afternoon (at approximately time 14.00hrs).

Methodological considerations

The present study only investigated the effect of TOD on cognitive test scores. Participants were not asked about their TOD preference, level of subjective tiredness, sleep patterns or the number of hours of sleep they had obtained the night before testing. As we did not ask participants about their TOD preference we did not take into consideration their peak arousal time. Although significant TOD effects have been noted it is important to consider other variables which impact on an individual's need for sleep or levels of tiredness. For example, amounts of daily exercise, dietary patterns, medication use, medical comorbidities, caffeine consumption and stress levels.

Analysis of the two data sets did not show consistent TOD effects for certain tests. For example, MMSE and TOD effects were only noted in data set two and not data set one. Likewise, significant TOD effects were noted for the PCS and LCS in data set one and not

two. These contradictions are likely to be due to differences in the two cohorts, most importantly participants in data set two had been asked to abstain from CCFS 12 hours prior to assessment and alcohol 24 hours prior. This was not the case for participants in data set one.

Conclusion

Novel observations reported here show that TOD has a significant influence on performance of the elderly in neuropsychological tests. For example, for data set two those participants completing the MMSE in the afternoon perform significantly worse than those taking the assessment in the morning. To our knowledge no previous studies have noted TOD effects for brief tests of general cognitive ability such as the MMSE and the MoCA.

The MMSE is currently one of the recommended cognitive tests by the NICE dementia guidelines which were updated in 2011 (NICE, 2011). The MMSE is, therefore, widely used in the general practitioner and hospital setting as a tool for dementia diagnosis. The score obtained on this test is considered when determining whether pharmacological intervention with anticholinesterase drugs is to be initiated (NICE, 2011). Previous research has highlighted potential problems with this test as it is not sensitive to mild degrees of cognitive impairment (Mitchell, 2009) and it was recommended that it not be used alone to diagnose MCI (Tombaugh & McIntyre, 1992) . For example, in a group of patients who converted to AD within the following 32 months their baseline MMSE score showed large variations of between 23-28/30 (Blackwell et al., 2004).

The fact that 200mg of caffeine (which is the equivalent to one medium filter coffee) was able to affect performance and interact with TOD further indicates the importance of

controlling for, or at least noting, the presence of external variables such as CCFS and TOD. For the GNT both the caffeine and placebo group show a linear decrease in performance with time but the caffeine sub-group perform significantly better. A possible explanation for the significant interactions between age, caffeine and TOD in data set two may be due to alterations (specifically a decline), in adenosine receptor expression with increasing age (Cunha, 2001). This may result in changes in the degree of adenosine antagonism that caffeine can induce. Further research is needed to confirm this.

The results presented here suggest that TOD and caffeine are important external factors to be controlled for in the diagnosis of a cognitive impairment in the elderly. The findings have particular relevance for research scientists and clinicians who are specifically involved in psychological assessment. Neglecting to consider these factors has clear clinical implications such as potential misdiagnosis and inaccurate assessment of decline in cognitive function. The influence of factors such as TOD and caffeine on performance strongly supports the recommendation that the results of neuropsychological testing of the elderly in clinical settings in which these, and other possibly relevant variables, are uncontrolled for, should be used with caution in diagnosis and treatment.

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