Measuring Information Processing Speed in Mild Cognitive Impairment: Clinical Versus Research Dichotomy

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Abstract. A substantial body of research evidence is indicative of disproportionately slowed information processing speed in a wide range of multi-trial, computer-based, neuroimaging- and electroencephalography-based reaction time (RT) tests in Alzheimer’s disease and mild cognitive impairment (MCI). However, in what is arguably a dichotomy between research evidence and clinical practice, RT associated with different brain functions is rarely assessed as part of their diagnosis. Indeed, often only the time taken to perform a single, specific task, commonly the Trail making test (TMT), is measured. In clinical practice therefore, there can be a failure to assess adequately the integrity of the rapid, serial information processing and response, necessary for efficient, appropriate, and safe interaction with the environment. We examined whether a typical research-based RT task could at least match the TMT in differentiating amnestic MCI (aMCI) from cognitively healthy aging at group level. As aMCI is a heterogeneous group, typically containing only a proportion of individuals for whom aMCI represents the early stages of dementia, we examined the ability of each test to capture intra-individual variation in performance. The results indicate that as well as significant slowing in performance of the operations involved in TMT part B (but not part A), individuals with aMCI also experience significant slowing in RT compared to controls. The results also suggest that research-typical RT tests may be superior to the TMT in differentiating between cognitively healthy aging and aMCI at group level and in revealing the performance variability one would expect from an etiologically heterogeneous disorder such as aMCI.

Keywords: Dementia, information processing speed, mild cognitive impairment, reaction time

INTRODUCTION

Although information processing speed tends to slow with age [1], disproportionate slowing appears related to cognitive limitations [2–5] and a wide range of brain disorders [6], including degenerative brain changes such as Alzheimer’s disease (AD) [6–10], vascular dementia [11], vascular cognitive impairment [12, 13], cerebral small vessel disease [14], amnestic mild cognitive impairment (aMCI) and its conversion to dementia [8] and faster decline in AD progression [15, 16].

Behaviorally, as reaction time (RT) is an important factor in relation to the integrity and efficiency of brain functions such as those involved in attention, cognition, and perception, it may provide a...
Clinically, despite this research evidence, information processing speed tends not to be assessed using a variety of function-specific, computer-based, multi-trial RT tests. Although a variety of RT-based tests are available and in use clinically, in some cases information processing speed is assessed by measuring the time taken to perform a given task, namely using a stop-watch to measure the single trial performance of the pen and paper Trail Making Test (TMT) [32–38]. The TMT is a test administered in two parts. In Trails A, individuals are required to connect a series of consecutively numbered circles that are presented in a random pattern on the paper: a task typically described as probing functions such as speed of processing in relation to attention, visual scanning and search, number recognition, numeric sequencing, and motor speed. In Trails B, individuals are required to connect a series of numbered and lettered circles alternating between the two sequences; a task typically described as probing the efficiency of set shifting, mental flexibility, executive function, divided attention, attention switching, visual search set shifting, simultaneous maintenance of two sequences, working memory and cognitive flexibility; arguably a measure of information processing speed in relation to multiple high level, non-specific functions [33, 34, 39]. TMT performance, in both parts A and B, is evaluated by scoring the time for completion in seconds, using one trial only.

Although research indicates that TMT performance, as in RT, is slower in older compared to younger adults [33, 40], with additional slowing related to pathological aging such as MCI, AD [41, 42], and vascular dementia [43] (but see also [10, 15, 21, 41, 44–54]), there are potential limitations associated with the clinical use of the TMT. Although Trails
information processing and response, possible with the use of RT tests. RT tests arguably provide more ‘data rich’ results than the TMT, and more the fact that the TMT is pen and paper based means that it is difficult to use its format in conjunction with neuroimaging studies and many other imaging studies and research. It can be shown that the potential for outcome variability between studies of processing speed in such populations [8, 70, 71], relates to underlying physiology (although see Müller et al. [36] and Hagen et al. [8]).

Arguably, in the time it takes to administer the TMT, a highly sophisticated and function-specific RT test (and one typically used in research and specifically that is used in a series of previous studies by Tales and colleagues (e.g., [8]), in which RT to a target appearing in isolation is compared to the time taken to respond to the same target when it is surrounded by distracting information. These tasks are similar to Trails B and Trails A, which are generally assumed to involve complex and higher processing levels and varying loads, attention shifting, eye movements, sequencing, suppression and inhibition of irrelevant or previously attended locations and stimuli, but unlike the TMT, numerous trails are presented in quick succession (as described in the methods section to follow). We examine in the first instance whether the visual search based RT tests can at least match the ability of the TMT to differentiate aMCI from cognitively healthy aging at group level. Secondly, as aMCI is a clinically heterogeneous group typically containing a proportion of individuals for whom it is a temporary condition, we examine the ability of each test to provide intra-group variation in performance. As both disproportionately slower task-completion time and RT are related to the presence of dementia, one would expect to see some performance variability within the aMCI but not the cognitively healthy control group in both tests.

Research has also indicated that in older adults both age and educational level can influence TMT performance, although outcome appears to vary with respect to TMT scoring methods, type of analysis, and RT variability test (and one typically used in research and specifically that is used in a series of previous studies by Tales and colleagues (e.g., [8])).

We address this question by investigating two measures commonly used as indicators of processing speed in aMCI and AD, namely the TMT, sometimes used in clinical assessment, and the RT component of a form of visual search test commonly employed in research and specifically that is used in a series of previous studies by Tales and colleagues (e.g., [8]), in which RT to a target appearing in isolation is compared to the time taken to respond to the same target when it is surrounded by distracting information. These tasks are similar to Trails B and Trails A, in that they are generally assumed to involve complex and higher processing levels and varying loads, attention shifting, eye movements, sequencing, suppression and inhibition of irrelevant or previously attended locations and stimuli, but unlike the TMT, numerous trails are presented in quick succession (as described in the methods section to follow). We examine in the first instance whether the visual search based RT tests can at least match the ability of the TMT to differentiate aMCI from cognitively healthy aging at group level. Secondly, as aMCI is a clinically heterogeneous group typically containing a proportion of individuals for whom it is a temporary condition, we examine the ability of each test to provide intra-group variation in performance. As both disproportionately slower task-completion time and RT are related to the presence of dementia, one would expect to see some performance variability within the aMCI but not the cognitively healthy control group in both tests.

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Participants
ded according to the principles of Helsinki. It was approved by the Frenchay Research Ethics Committee and all participants gave written informed consent to participate. Only individuals with the capacity to consent were part of this research, 48 older adults with mild cognitive impairment and 39 cognitively healthy older adult controls. The demographic details are shown in Table 1.

The cognitively healthy older adult and the aMCI+ groups did not differ significantly with respect to mean Age \([Z = -1.65, p = 0.098]\) or mean Educational level \([Z = -0.53, p = 0.6]\), indicating that attempts at matching these demographics between groups was successful. However, the NART score (level of pre-morbid intelligence) was significantly poorer for the aMCI+ compared to the cognitively healthy older adult group \([Z = -3.3, p = 0.001]\). As expected, MMSE score was significantly lower for the aMCI+ compared to the cognitively healthy older adult group \([Z = -2.98, p = 0.003]\).

Experimental task and procedure

In a counter balanced procedure, the TMT (both Trails A and Trails B) and the visual search task (both target alone and target plus distracter conditions) were administered to all participants by a trained psychometrist. Testing took place within the Bristol Memory Disorders Clinic.

The pen and paper TMT

When administering Trails A, the psychologist provided the participants with a practice sheet as a way of visually explaining the task. Once the participants completed the practice sheet, they completed the full Trails A. For this task the participants were instructed to draw one continuous line joining a series of circled numbers in ascending order on a sheet of paper as fast as they could. A time limit of 5 minutes is stipulated for this task. Scores are based on the number of seconds until completion and are compared to the cognitively healthy older adult group. For this task, none were classed as anxious or depressed. All participants performed a typical Bristol Memory Disorders clinic battery of neuropsychological tests including Mini-Mental State Examination (MMSE) [72], WAIS-III (Wechsler Intelligence Scale) subtests (digit span, vocabulary, arithmetic, picture completion) [73], Hopkins Verbal Learning Test-Revised [74], CLOX (executive function) [75], Visual Form Discrimination (VFD) [76], S-word fluency and Neurological or psychiatric condition (see Phillips et al. [8] and [80, 81]). In total, 87 individuals took part in this research, 48 older adults with mild cognitive impairment and 39 cognitively healthy older adult controls. The demographic details are shown in Table 1.
tasks participants are immediately informed and they correct them. Errors like this were accounted for in the time to complete the task or if they failed to complete the task in the allotted time.

**Visual Search Task**

The task used was one employed in several previous studies by Tales and colleagues [8, 80, 81, see also 7], in which the time taken to respond to a target (namely to discriminate whether an arrow pointing to the left or right) when it appeared in isolation upon the computer screen was compared with the time taken to respond to the same target when it was surrounded by similar but irrelevant and distracting stimuli was determined. This paradigm was presented on a Toshiba Satellite-Pro lap top computer viewed at a distance of 57 cm. Superlab software (Cedrus Corporation San Pedro, CA) was used for stimulus presentation and response capture. This choice RT task included a black target, either a right or left-pointing arrow head; with participants required to indicate whether the arrow was pointing to the left or right. The distracting stimuli consisted of seven black arrow-heads pointing up or down. A ‘clock-face’ configuration was used to position the target, both when alone and when surrounded by distractors, in a counterbalanced arrangement in order to eliminate any visual field position-related differences in processing. The target appeared eight times at each of the possible ‘clock-face’ locations giving a total of sixty-four trials. Distractors were presented for half the trials. On each trial the central fixation cross appeared on screen for 1000 ms prior to the appearance of the target and remained on screen for the duration of the trial. The stimuli remained on screen until a response was made. Participants were instructed to fixate on the center cross at the beginning of each trial and to respond as quickly but as accurately as possible as to whether the target was pointing to the right or left by pressing one of two computer keyboard keys. After instruction, all participants were asked to explain the task to the researcher in order to demonstrate that they fully understood the task and then performed approximately 10 practice trials. The ability of the participants to fixate upon the central cross was checked at the beginning of each trial by researcher observation. The researcher was also in a position to record any lack of trial response and to prompt re-engagement of the task. Participants received no performance-feedback during testing.

**DATA ANALYSIS AND RESULTS**

Group mean analysis for RT speed was based on the mean values (of correct trials only) for each individual within the group. The mean response times for TMT, Trails A and B, and the mean RTs (ms) for the target alone and the target plus distracter search are displayed in Table 3, together with the corresponding standard deviation and standard error of the mean. Note that in the TMT, no participants exceeded the five-minute time limit. For the visual search tasks, only correct trials were included in the statistical analysis. Accuracy was high; the mean percentage of errors overall was low for both the cognitively healthy (3.2%) and aMCI+ (4.6%) groups with no evidence of speed accuracy trade off effects. No participants failed to respond to a trial and none required prompting.

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Education</th>
<th>Age</th>
<th>NART</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitively healthy older adults (n = 39)</td>
<td>Mean 14.56</td>
<td>70.5</td>
<td>118.3</td>
<td>27.1</td>
</tr>
<tr>
<td>SD</td>
<td>3.1</td>
<td>8.3</td>
<td>8.1</td>
<td>1.5</td>
</tr>
<tr>
<td>SEM</td>
<td>0.49</td>
<td>1.3</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>at (n = 48)</td>
<td>Mean 14.46</td>
<td>67.6</td>
<td>111.8</td>
<td>25.9</td>
</tr>
<tr>
<td>SD</td>
<td>3.72</td>
<td>8.6</td>
<td>16.6</td>
<td>1.8</td>
</tr>
<tr>
<td>SEM</td>
<td>0.54</td>
<td>1.2</td>
<td>2.4</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Table 2
Normality of distribution (Shapiro Wilkes test)

<table>
<thead>
<tr>
<th></th>
<th>OLD statistic df Sig.</th>
<th>OLD statistic df Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.939 39 0.036</td>
<td>0.941 48 0.017</td>
</tr>
<tr>
<td>Education</td>
<td>0.953 39 0.104</td>
<td>0.911 48 0.002</td>
</tr>
<tr>
<td>NART</td>
<td>0.924 39 0.012</td>
<td>0.764 48 0.000</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.950 39 0.085</td>
<td>0.932 48 0.008</td>
</tr>
<tr>
<td>Search: target alone</td>
<td>0.911 39 0.005</td>
<td>0.944 48 0.022</td>
</tr>
<tr>
<td>Search: target &amp; distracters</td>
<td>0.949 39 0.077</td>
<td>0.911 48 0.001</td>
</tr>
<tr>
<td>Trails A</td>
<td>0.973 39 0.459</td>
<td>0.942 48 0.019</td>
</tr>
<tr>
<td>Trails B</td>
<td>0.833 39 0.000</td>
<td>0.822 48 0.000</td>
</tr>
</tbody>
</table>

For Trails A, analysis revealed no significant difference in group-mean response time (in seconds) between cognitively healthy aging and aMCI+ [Z = –1.4, p = 0.16]. Note, however, that whereas Trails A performance was normally distributed for the cognitively healthy older adult group, this was not the case for the aMCI+ group. Note also that multiple correlational analysis (with Bonferroni correction) failed to reveal any correlation of response time with age, education, NART score, or MMSE score in either group [all p-values >0.05].

For Trails B, mean response time was significantly slower in aMCI+ compared to cognitively healthy aging [Z = –1.96, p = 0.05; effect size (r) = 0.21]. For both groups, performance of Trails B was not normally distributed and multiple correlational analysis (with Bonferroni correction) failed to reveal any correlation of response time with age, education, NART score, or MMSE score in the older adult group [all p-values >0.05] and education, NART score, or MMSE score in the aMCI+ group [p-values >0.05], although performance of Trails B in the aMCI+ group was significantly correlated with age [r = 0.522, p < 0.001 which survives Bonferroni correction; p = 0.004].

Visual search target alone and target plus distracter reaction time analysis
Mean RT in response to the target alone Visual Search task was significantly slower for the aMCI+ compared to cognitively healthy aging.
Table 3

<table>
<thead>
<tr>
<th>Trails A</th>
<th>Trails B</th>
<th>Search Target alone</th>
<th>Search Target &amp; distracters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean response time (s)</td>
<td>Mean response time (s)</td>
<td>Mean RT (ms)</td>
<td>Mean RT (ms)</td>
</tr>
<tr>
<td>SD 10.4</td>
<td>34.7</td>
<td>744.2</td>
<td>1730.6</td>
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<tr>
<td>SEM 1.7</td>
<td>5.6</td>
<td>27.7</td>
<td>64.5</td>
</tr>
<tr>
<td>SD 40.6</td>
<td>98.2</td>
<td>861.1</td>
<td>2230.4</td>
</tr>
<tr>
<td>SEM 2.0</td>
<td>7.5</td>
<td>30.2</td>
<td>102.5</td>
</tr>
</tbody>
</table>

DISCUSSION

The TMT is sometimes used clinically to assess the speed of information processing in dementia, MCI, and related disorders, by measuring the time taken to complete the task of consecutively joining a series of numbers and or letters on a sheet of paper. However, in research terms, speed of information processing is generally described with respect to reaction time, i.e., the time elapsed between the relatively rapid presentation of a stimulus and the behavioral response, measured over a number of trials at relatively short intervals. Arguably, the processing involved in processing and responding to such rapid and repeated stimuli is different from that involved in performing the TMT, and we suggest that measuring RT may indeed be more akin to, ecologically valid or relevant with respect to the investigation of the integrity of information processing speed related to everyday tasks which typically require rapid processing, decision making, and response.

However, although RT tests may, in theory, represent a clinically valid replacement of the TMT, we have not been able to identify any evidence investigating the performance of the TMT compared to the aMCI group. RT was not normally distributed and was not correlated with educational level [Z = 0.44], further analysis revealed, however, that RT was not normally distributed and was not correlated with educational level [Z = 0.44]. Further, as aMCI represents the early stages of a dementia process, a proportion of individuals for whom it remains of unknown etiology and others for whom it is a temporal disorder, aMCI is a clinically heterogeneous group, in an attempt to determine whether the visual search based RT tests can at least be a clinically valid replacement of the aMCI group.
examined the ability of each test to provide intra-group variation in performance. As both slower task-completion time and the presence of dementia, one would expect to see some performance variability within the cognitively healthy control group. Nevertheless, the effect size of the significant difference in performance between the two groups was greater than that for the Trails B test (effect size ‘r’ = 0.21 and 0.3), respectively.

For the target plus distracter visual search task, mean RT was significantly slower in aMCI+ compared to cognitively healthy aging. The effect size of this outcome (r = 0.38) was greater than that exhibited for the target alone search (r = 0.3) and the Trails B (r = 0.21) tasks, indicating that the target plus distracter visual search task is the one most sensitive to aMCI+. Furthermore, whereas the distribution of RT performance was normal within the cognitively healthy older adult group for the target plus distracter visual search task this was not the case for the aMCI+ group, revealing instead a number of considerably slower responses, i.e., outliers (see the Box plot in Figs. 2 and 3, and Table 2). There is, of course, once again some degree of overlap between performance in the control and the patient group and therefore not everyone with aMCI+ reveals slower mean RT compared to cognitively healthy aging. It appears rather that the aMCI+ group contains a greater proportion of individuals with disproportionately slower, responses. However, unlike Trails A, Trails B, and the simple target alone visual search RT task, the target plus distracter visual search RT task promotes outliers, i.e., disproportionately slowed responses only within the aMCI+ group. It may be the case that this RT task does not produce as many ‘false positives’ i.e., disproportionately poor performance within the control group, as does the target alone search RT task and the Trails B test. Note also that three individuals in the aMCI+ group are outliers in both the Trails B and the target plus distracter visual search RT test. This may indicate...
present a decline to dementia if administered to an individual over the follow up of all the participants in this way from making such an analysis. Thus within the aMCI may, however, in part, some of the disparity between previous studies, as slow-ness to specific etiologies of aMCI+ that have a neurodegenerative basis. However, that a proportion of individuals have very slow RTs, much beyond cognitively healthy aging, individuals processing related to Shy decades in the environment and situations that require serial, rapid, and continuous processing, and response can be timed. These effects are of potential significance irrespective of whether an individual with early stages of dementia or not.

Gender, IQ (NART), and MMSE

Gender difference in performance was observed in the aMCI+ group. RT was significantly faster for males than females for the targeted search group. Although there was a lower educational level for males than females group, which may have potentially contributed to this result, there was no significant gender educational level in either males or females. A gender-related effect should be evident in the targeted search task RT only. Nevertheless, the results indicate that within the same processing speed outcome and its relationship occurs only when a wider range of ages is included. In contrast, although performance of Trails B was not significantly correlated with age in the control group, it was significantly correlated with age (surviving Bonferroni correction) in the aMCI+ group: a finding which if further research finds to be robust, may have implications for the interpretation of results over this age range. The finding that age is not similarly correlated with performance in both cognitively healthy aging and aMCI+ also breaks an assumption necessary for covariate analysis (if parametric analysis of RT data is attempted; another reason why we used non-parametric testing for our results). In contrast to Trails A and B, RT of both versions of the visual search task was not significantly correlated with age for either the cognitively healthy older adult or the aMCI+ group.

Performance of Trails A, B, and both versions of the visual search RT task was not significantly correlated with educational level for either the cognitively healthy older adult or the aMCI+ groups (although there was some evidence of a correlation for Trails A performance and education for the aMCI+ group it did not survive Bonferroni correction). Although the aMCI+ group had a significantly lower IQ (NART score), explained by the lower score for females compared to males in this group, performance of none of the four tasks was significantly correlated with IQ. Performance of TMT and both visual search tasks was not significantly correlated with MMSE (note however that for the aMCI+ group, Trails B was significantly correlated with MMSE score but again this did not survive Bonferroni correction).

There is therefore some room for debate about whether some relatively small effects of age and educational level on RT in the aMCI+ group are of sufficient magnitude to be meaningful.
limitations

Unfortunately we were unable to follow up both groups in order to determine clinical outcome thus precluding analysis of whether those individuals with outlying response times and RTs in the aMCI + group were most likely to develop dementia. Furthermore, the results and thus their potential interpretation is limited by the fact that we did not test repeatedly and over various time periods, we would have combined our behavioral data from the imaging study in order to determine the relationship between our RT and response speed measures at a group and individual level. We would have also explored the impact of methodological manipulations such as time pressure, processing load, and various types of distraction in order to explore the role and range of information processing deficits in aMCI +

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dementia: Short fixations but long reaction times. 

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cortical vascular dementia: Short fixations but long reaction times. 


