Intra-Individual Reaction Time Variability in Mild Cognitive Impairment and Alzheimer’s Disease: Gender, Processing Load and Speed Factors

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Abstract

Compared to cognitively healthy ageing (CH), intra-individual variability in reaction time (IIV_{RT}), a behavioural marker of neurological integrity, is commonly reported to increase in both Alzheimer’s disease (AD) and mild cognitive impairment (MCI). It varies in MCI with respect to whether it represents the pro-dromal stages of dementia or not; being greatest in those most likely to convert. Abnormal IIV_{RT} in MCI therefore represents a potential measure of underlying functional integrity that may serve to differentiate MCI from CH and to help identify those patients for whom MCI is the result of a progressive pathological process. As the clinical approach to MCI is increasingly stratified with respect to gender, we investigated whether this factor could influence study outcome. The influence of RT_{SPEED} and processing load upon IIV_{RT} was also examined. Under low processing load conditions, IIV_{RT} was significantly increased in both MCI and AD compared to CH. However, correcting for an individual’s processing speed abolished this effect in MCI but not in AD, indicating that the increased IIV_{RT} in MCI and AD may result from different factors. In MCI but not in CH, IIV_{RT} was significantly greater for females. Increasing task processing load by adding distracting information, although increasing overall IIV_{RT}, failed to improve the differentiation between CH and both MCI and AD, and in MCI resulted in a reduction in the influence of gender upon study outcome. The outcome of studies investigating IIV_{RT} in MCI and AD compared to CH therefore appear influenced by the gender of the participants, by task-related processing load and processing speed.

Introduction

A behavioural measure of increasing interest in the study of mild cognitive impairment (MCI) and dementia is the intra-individual variability of reaction time (IIV_{RT}) over the trials of a given task. This measure appears to be a behavioural indicator of neurological integrity, as a growing number of studies link IIV_{RT} to structural and functional brain characteristics. Indeed, DTI (diffusion tensor imaging) indicates a relationship between IIV_{RT} and white matter integrity, with increased variability indicative of white matter degradation, disconnectivity in associative pathways and brain dysfunction [1–11]. A wide range of behavioural studies now indicate changes in reaction time variability above and beyond slowing, with increased inconsistency linked with healthy ageing, impaired top-down executive and attentional control processes, cognitive disorder, neurotransmitter dysfunction, fatigue, stress [4], [6], [11–22] and various neurological, degenerative and psychiatric disorders including Parkinson’s disease [23–26], multiple sclerosis [27], schizophrenia [28] and brain injury [29], [30] and dementia [18]. Thus, behaviourally measured relative variability is a fruitful measure for the characterisation of healthy-ageing and pathological change.

Compared to cognitively healthy ageing (CH), IIV_{RT} is commonly reported to increase in both Alzheimer’s disease (AD) and MCI and to vary in MCI with respect to whether it represents the pro-dromal stages of dementia or not; being greatest in those most likely to convert [2], [3], [6–9], [12], [13], [15–17], [31–39]. Abnormal IIV_{RT} in MCI therefore represents a potential measure of underlying functional integrity that may serve to help identify those patients for whom MCI is the result of a progressive pathological process. Furthermore, the relationship between high IIV_{RT} and the breakdown in the integrity of information processing indicates its potential as an adjunct to neuropsychological assessment and the identification of those at risk of a greater degree of functional and behavioural impairment. However, although a measure of IIV_{RT} can be quickly and easily obtained under normal clinical conditions, its interpretation into the clinical applicability of IIV_{RT} is hindered by a degree of variability in study outcome and the interpretation of results (see [19] for a review). Although disparity in methodology and data analysis is a
continually postulated causal factor, substantial individual differences in patients and controls also exist, both within and between studies. As a more individual or stratified approach is increasingly applied to the diagnosis and treatment of MCI [40] adopting a corresponding research approach to IIV$_{RT}$ is therefore necessary to ensure outcome validity and relevance and it is the potential for some of these factors to affect study outcome that we explore in the present study. One of these factors is gender.

Gender is acknowledged as an important factor in clinical research in general and emerging evidence indicates that it may be of relevance with respect to the incidence, prevalence, risk profile, age-of-onset, effects, symptoms and severity of disease in MCI and AD e.g. [20], [40–46]. Many aspects of cognition and attention, together with some of the tests used for the diagnosis, staging and follow-up of MCI and AD, are also influenced by gender [40], [46–57]. White matter micro-architecture and cortico-cortical projections, with which the behavioural measure of IIV$_{RT}$ is associated, may also be influenced by gender, although some of these differences appear to be specific and/or inconsistent [1], [40], [43], [44], [46], [49], [52], [58], [59–65]. Such evidence increases the likelihood that clinically relevant gender-related factors arise in the investigation of IIV$_{RT}$ in MCI, AD and CH. A common assumption in ageing, MCI and AD-related research is that any gender effects related to IIV$_{RT}$ would be similarly expressed in patients and controls and, consequently, that simply ensuring similar ratios of males to females in the study groups would balance out any gender-related influence. In the present study we address this assumption by examining whether gender-related IIV$_{RT}$ effects are expressed similarly in CH and MCI. In order to avoid potential confounds in the behavioural examination of gender related effects in IIV$_{RT}$ in patients and controls it is imperative that the males and females within each group are matched with respect to cognitive function, diagnosis and demographic factors. Thus, in our study examining IIV$_{RT}$ in CH and MCI the men and women within each group were matched as closely as possible in terms of age, pre-morbid IQ, MMSE score and z-score of a range of neuropsychological tests of memory, language, perception and executive function and diagnosis. A contentious issue in this area of research is the relationship between processing or reaction time speed (RT$_{SPEED}$) and IIV$_{RT}$. Typically, RT$_{SPEED}$ and IIV$_{RT}$ are highly correlated to one another and in some instances raised IIV$_{RT}$ appears to result simply from a correspondingly slowed RT$_{SPEED}$ and debate continues with regards to whether IIV$_{RT}$ that can be explained by slowing is clinically useful e.g. [2]. However, evidence that both RT$_{SPEED}$ and IIV$_{RT}$ are associated with neurological integrity, neurodegeneration, cognitive status and gender [1–3], [11], [19], [65–72] indicates that both measures may provide clinically relevant information. The fact that a significant group difference in IIV$_{RT}$ might disappear when RT$_{SPEED}$ is taken into account may simply indicate that, with respect to a particular task, the raised IIV$_{RT}$ can be explained by RT slowing, but the fact remains that the slowing may itself be indicative of some degree of neurological disruption. To speculate further, whether or not slowed RT is the cause of increased IIV$_{RT}$ in the study of MCI and dementia may be related to disease stage, i.e., a result of factors such as pathological burden, neurological and cognitive breakdown, aetiology and the presence or not of pro-dromal or frank dementia. A threshold of structural and functional integrity may exist: below which RT slowing is the main behaviourally observable change and the main contributory factor to an increase in IIV$_{RT}$: above which, raised IIV$_{RT}$ is the result of additional and possibly RT-independent neurological damage. We suggest therefore that in the absence of frank dementia, i.e., in MCI, raised IIV$_{RT}$ is likely to be explained by concomitant slowing, whereas in AD, i.e., in dementia, it is not. Thus, in preliminary exploration of this idea, we examine IIV$_{RT}$ with respect to RT$_{SPEED}$ in both MCI and AD in the present study.

Whatever, the underlying cause, increased variability may still adversely affect information processing and thus behaviour and indicate the presence of neurological disruption. Nevertheless, whether or not adjustments are made for RT$_{SPEED}$ can determine whether or not IIV$_{RT}$ is reported as significantly greater in MCI and dementia than in CH [11], [15], [19], [31], [35], [63] and whether gender related effects in IIV$_{RT}$ are expressed or not [19], [49], [65]. Thus in the present study, we analyse both raw and RT$_{SPEED}$-adjusted IIV$_{RT}$ data in CH, MCI and AD in order to determine its effects upon study outcome and interpretation. Furthermore, although there is some evidence to suggest that it is IIV$_{RT}$ rather than RT$_{SPEED}$ that best differentiates both MCI and AD from CH, this is not always so [12], [15–17], [31], [32], [35] and RT$_{SPEED}$ in its own right forms a substantial research area in ageing, MCI and dementia e.g. [12], [31], [73–75]. Consequently we also examine RT$_{SPEED}$ per se in order to determine whether it is RT$_{SPEED}$ or IIV$_{RT}$ that results in the greatest group differentiation between CH and MCI and between CH and AD.

Methodologically, IIV$_{RT}$ in ageing and dementia-related research has been examined using a wide range of paradigms. Following the general assumption that tasks with more complex or higher processing loads allow the accumulation of decline across multi-component processes [76] and are thus more likely to differentiate between CH and MCI and CH and AD, the majority of the tests used to measure IIV$_{RT}$ have been described as having high processing, attentional or cognitive demands [2], [6], [12], [16], [17], [19], [65], [77]. However, such tests are difficult to compare and to quantify as they can vary not only in terms of the resources required to process the information contained in the RT task, but also with respect to the decision and motor components of the task response. Furthermore, simple tests can provide superior differentiation [6], [77]. It is likely therefore that the task used to examine IIV$_{RT}$ has a substantial bearing on study outcome in clinical populations. To investigate this we employ a computer-based visual search task [78] in which the same decision and motor requirements for the target RT response are maintained under both low (target alone) and high (surrounding the target with distracting information) processing resource demands, see [31], [78]. The ‘target in isolation’ condition represents a typical computer-based visual choice RT task. Surrounding the same target with distractors of a similar form but differing orientation simulates the cluttered environment more typical in visual processing, in which more component processes, such as attention shifting, eye movements and the suppression or inhibition of irrelevant information, are required in order to find the target, thus slowing response time.

Debate also continues regarding which measure of intra-individual variability is used, i.e. standard deviation (SD) or inter-quarile range (IQR) e.g. see [19] for a review and which measure of processing speed is used, i.e. mean or median RT, and whether the inclusion or not of aberrant responses affects RT$_{SPEED}$ and IIV$_{RT}$. In order to examine these potential sources of study outcome variation, we measure individual RT$_{SPEED}$ using both median and mean values and IIV$_{RT}$ using both IQR and SD values with analysis performed both with and without the RTs responses for error trials.

To summarise, here we explore the potential influence of gender, RT$_{SPEED}$, task processing demands, the unit of measurement and the inclusion or not of error responses, upon the study of
In a group of patients highly typical of individuals presenting to memory clinics, namely those with amnestic multi-domain mild cognitive impairment (aMCI). In a further study RT SPEED and IV RT is examined in probable AD compared to CH. The relationship between RT SPEED and IV RT in MCI and probable AD compared to cognitively healthy ageing is also examined.

**Study 1. Comparing IV RT in Amnestic Multi-domain Mild Cognitive Impairment and Cognitively Healthy Ageing**

**Methods**

**Ethics statement.** This study was conducted according to the principles in the Declaration of Helsinki. It was approved by Frenchay Research Ethics Committee and all participants gave written informed consent to participate. Only individuals with the capacity to consent were included. Capacity to consent was assessed by the clinician [JH] with specialist expertise in this field and consistent with the requirements of the Mental Capacity Act.

**Participants.** In line with the expected overall large effects for our study, based on previous research, the a-priori estimate of participant numbers was based on a statistical power level of 0.8, an anticipated effect size [Cohen’s d] of 0.7, and a probability level of 0.05, and revealed that, for two-tailed analysis, an approximate minimum total sample size of 68, with a minimum sample size per group of 34, was required.

Community dwelling cognitively healthy older adults (n = 62) and patients with aMCI (n = 55) were recruited through the Bristol Memory Disorders Clinic. All participants had normal or corrected-to-normal vision. Although medication could not be controlled in either group, none of the participants were receiving medication deemed likely to affect cognitive or attention-related function and none of the participants were receiving drug treatment or behavioural intervention of any kind for their cognitive dysfunction.

All participants performed a range of tests forming the typical Bristol Memory Disorders Clinic battery of neuropsychological tests that included MMSE [79], Wechsler Adult Intelligence Scale-III subtests [80], Hopkins Verbal Learning Test-Revised [81], CLOX [82], Visual Form Discrimination Task [83], National Adult Reading Test [NART [84], S-word fluency and Animal fluency [85], Story Recall [Adult Memory Information Processing Battery [86], BADLS [87] and BASDEC (screen for depression) [88]. The CH adults had to perform at an age-appropriate level (z-score above −1.5) on all tests. All aMCI patients had self-reported change in memory, corroborated by an informant and objective decline, namely individual z-scores equal or less than −1.5 in memory and at least one other area of function, in the absence of dementia and an intact ability to perform activities of daily living (assessed using BADLS). Exclusion criteria included past history of serious head injury, stroke or other significant neurological or psychiatric condition. The clinical and demographic details for the CH and aMCI are shown in Table 1.

The CH and aMCI groups did not differ significantly with respect to mean age [t (df 115) = 1.03, p = .31]. NART score was significantly poorer in the aMCI compared to the CH group [t (df 98.1) = 4.54, p < .001, effect size (Cohen’s d) = .77] and, as to be expected, mean MMSE score was significantly lower in the aMCI compared to the CH group [t (df 115) = 4.51, p < .001]. Within the CH group, male and female participants did not differ with respect to mean age [t (df 60) = .44, p = .66], NART [t (df 60) = .19, p = .85] or MMSE, [t (df 60) = .77, p = .45]. Within the aMCI group, male and female participants did not differ with respect to mean age [t (df 53) = .95, p = .35], NART [t (df 53) = 1.43, p = .16] or MMSE [t (df 53) = .016, p = .99]. Note that here and throughout the manuscript df denotes the degrees of freedom correction used when equal variances cannot be assumed.

**Stimuli and tasks.** Participants were asked to perform a simple computer-based visual search task and one used in several previous studies e.g. [70] in which the time taken to respond to a target (target discrimination) when it appeared in isolation upon the screen and the time taken to respond to the same target when it was surrounded by similar but irrelevant and distracting stimuli was determined. This paradigm [78] was presented on a Toshiba Satellite-Pro laptop computer viewed at a distance of 57 cm. Stimulus presentation and response recording was performed using Superlab software (Cedrus Corporation San Pedro, CA). All trials included a black target that was either a left or right-pointing arrow, i.e., a choice RT task. The task was to indicate whether the arrow was pointing to the right or left. The distracting stimuli consisted of seven black arrows that pointed up and down. A ‘clock-face’ configuration (see Fig. 1) was used to position the target, both when it appeared alone and when surrounded by 7 distracters, in a specific counterbalanced arrangement in order to eliminate any differences in processing between right and left and upper and lower visual fields. A total of 64 trials were presented; the target appearing 8 times at each of the possible ‘clock-face’ locations. For one half of the trials distracters were presented at the other locations and for the other half no distracters were presented. For each trial the central fixation cross appeared on screen for 1000 ms prior to the appearance of the target (with or without distracters) and remained on screen for the duration of the trial. The stimuli remained on screen until the participant responded, after which the fixation point appeared again. The participants were instructed to fixate on the centre 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 requirements of the task and then to perform a practice block of approximately 10 trials. The ability of the participant to fixate on the cross at the beginning of each trial continued to be checked throughout the procedure by researcher observation. The participants received no feedback about their performance during the test [78].

Group mean analysis for RT SPEED was based on both the median and mean values for each individual within the group. Likewise, group mean analysis for IV RT was based on both the IQR [between 25th and 75th quartiles] and SD values for each
individual within the group using data both including and excluding error RT responses. However, to pre-empt our results, the inclusion or exclusion of error RTs, the use of mean or median measures of RTs, the use of SD or IQR measures of IIVRT, did not alter study outcome, with RTs and IIVRT remaining highly correlated to one another irrespective of how they were measured. Therefore, we report only the results for error-excluded median-based RTs and IIVRT and IQR-based IIVRT analysis. Parametric statistical analysis was applied to the data, with corrections made for conditions under which equal variances could not be assumed. To ensure a robust statistical approach non-parametric analysis was also applied to the data but this resulted in no change in study outcome, thus in line with common practice we report the parametric analysis.

The RTs, IIVRT and the coefficient of IIVRT in response to the target appearing in isolation constituted the low processing condition and can be seen in Table 2. For the increased processing load condition, the target alone RTs, IIVRT and the coefficient of IIVRT values were subtracted from those for the target plus distractors condition [target plus distractors – target alone], see Table 3. All analysis was performed at the two-tailed level.

Results

Low processing load conditions. Under low processing load conditions, the box-plots (Figures 2 and 3) and Table 2 reveal a greater degree of IIVRT and slower RTs for the aMCI group compared to the CH group. Pronounced gender-related effects within the aMCI group, together with greater within-group variability in IIVRT and RTs in aMCI compared to cognitively healthy ageing are also evident. Group mean RTs, was significantly slower in aMCI compared to CH [t(75.2) = 4.06, p<.001, effect size (Cohen’s d) = .78]. For the CH group, RTs was significantly correlated with age [r = .27, p = .037], but not with NART [r = −.114, p = .38], or MMSE [r = −.117, p = .36]. The same analysis for the aMCI group revealed that RTs was not significantly correlated with RT [r = .039, p = .78], MMSE [r = .021, p = .85] or age [r = .054, p = .7].

Group mean IIVRT was significantly greater in aMCI compared to CH [t(df 68.3) = 3.19, p = .002, effect size (Cohen’s d) = .65]. For the CH group IIVRT was not significantly correlated with NART [r = .08, p = .53], MMSE [r = −.063, p = .63] or age [r = .14, p = .28] and that similarly, for the aMCI group, IIVRT was not significantly correlated with NART [r = .056, p = .7], MMSE [r = −.075, p = .6] or age [r = .014, p = .92].

Converting the IQR measure of IIVRT to its coefficient, i.e., [IQR/median RTs ×100] eliminated the significantly greater IIVRT in aMCI compared to CH [t(df 83) = 1.78, p = .079]. The mean percentage of errors was low overall and did not vary significantly between CH and aMCI [t(df 96.6) = 1.87, p = .07].

With thanks to anonymous reviewers for suggesting further analysis, we examined RTs and IIVRT with respect to the neuropsychology test z scores for both groups. For the CH group, RTs was not significantly correlated with performance on any of the tests [all p-values >.05] and IIVRT was found to be significantly correlated only with semantic fluency performance [r = −.33, p = .01]. For the aMCI group both RTs and IIVRT were significantly correlated with performance on the Visual Form Discrimination Task [r = −.27, p = .045] and [r = −.3, p = .026] respectively, but not with the performance of any of the other neuropsychological tests. Note also that the significant outcomes do not survive Bonferroni correction.
Gender. In CH, neither IIVRT or RT SPEED differed significantly with respect to gender [t (df 60) = 0.43, p = .67] and [t (df 60) = 0.47, p = .64] respectively. For the females in the CH group, RT SPEED was not significantly correlated with NART [r = -.045, p = .81], MMSE [r = -.22, p = .25] or age [r = .26, p = .17] and likewise, IIVRT was not significantly correlated with NART [r = .047, p = .8], MMSE [r = .03, p = .87] or age [r = .03, p = .87].

We examined correlations between RT SPEED and IIVRT and neuropsychology test z scores separately for females and males and for both groups. For the females, neither RT SPEED or IIVRT was significantly correlated to any neuropsychological test score [all p-values >.05].

The difference [target plus distractors – target alone] in RTSPEED, (msec), IIVRT and corresponding IIVRT coefficient and percentage errors (standard deviation in parenthesis).

### Table 3. Data for each sample group.

|          | CH        |          |          |
|----------|-----------|----------|----------|
|          | Male (n = 31) | Female (n = 31) | All (n = 62) |
| RT speed |           |           |          |
|          | 923.7     | 1049.5   | 986.6    |
| IIVRT (IQRI) | 867.9 | 1072.0   | 970.0   |
| IIVRT Coef | 35.1     | 43.3     | 39.2    |
| % errors | -1.3%   | -0.3%    | -0.8%  |

The difference in RT speed and intra-individual variability between the high and low processing load conditions.

The difference [target plus distractors – target alone] in RT SPEED, (msec), IIVRT and corresponding IIVRT coefficient and percentage errors (standard deviation in parenthesis).

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\( p = .15 \) or the aMCI \(^+\) group \( t (df = 53) = 1.75, p = .09 \) respectively.

Similarly, the distracter-induced increase in mean II\( V_{RT} \) did not differ with respect to gender in the CH \( t (df = 60) = 1.46, p = .15 \) or the aMCI \(^+\) group \( t (df = 53) = 1.75, p = .087 \) respectively. For CH, converting IQR to its coefficient value did not alter the effect \( t (df = 60) = 1.41, p = .16 \) between males and females. For the aMCI \(^+\) group converting IQR to its coefficient value did not alter the effect \( t (df = 44.2) = 1.1, p = .28 \) between males and females. For the low processing load condition the mean percentage of errors was very low for both the CH and the aMCI \(^+\) groups and adding distracters actually resulted in an overall, but not significant, reduction in the mean percentage of errors made (denoted by the \( \% \) value in table 3) for the CH \( t (df = 61) = 1.36, p = .18 \) and for the MCI \( t (df = 54) = .39, p = .7 \) groups. As is evident from Tables 2 and 3 the mean percentage change in errors also did not vary significantly with respect to group, gender or task. And indeed as already highlighted the inclusion or exclusion of error-related data did not affect study outcome.

**Errors.** For the low processing load condition the mean percentage of errors was very low for both the CH and the aMCI \(^+\) groups and adding distracters actually resulted in an overall, but not significant, reduction in the mean percentage of errors made (denoted by the \( \% \) value in table 3) for the CH \( t (df = 61) = 1.36, p = .18 \) and for the MCI \( t (df = 54) = .39, p = .7 \) groups. As is evident from Tables 2 and 3 the mean percentage change in errors also did not vary significantly with respect to group, gender or task. And indeed as already highlighted the inclusion or exclusion of error-related data did not affect study outcome.

**Study 2: Comparing RT\( SPEED \) and II\( V_{RT} \) in Alzheimer’s Disease and Cognitively Healthy Ageing**

As described in the introduction, several previous studies comparing probable AD to CH have shown significantly raised

RT\( SPEED \) and significantly slower II\( V_{RT} \) in probable Alzheimer’s disease compared to CH. However, as in aMCI \(^+\), variability in AD-related study outcome exists, particularly with respect to how II\( V_{RT} \) is measured. In view of the importance of replicability in research we examine the status of RT\( SPEED \) and II\( V_{RT} \) in AD compared to CH. As in our study of aMCI \(^+\), group mean analysis for RT\( SPEED \) was based on both the median and mean values for each individual within the group. Similarly, group mean analysis for II\( V_{RT} \) was based on both the IQR [between 75\(^{th}\) and 25\(^{th}\) quartiles] and SD values for each individual within the group, using data both including and excluding error RT responses. However, to pre-empt our results, the inclusion or exclusion of error RTs, the use of mean or median measures of RT\( SPEED \) and the use of SD or IQR measures of II\( V_{RT} \) did not alter study outcome, with RT\( SPEED \) and II\( V_{RT} \) remaining highly correlated to one another irrespective of how they were measured. Therefore, we report only the results for error-excluded median-based RT\( SPEED \) and IQR-based II\( V_{RT} \) analysis. Furthermore, in the introduction we suggested that slowed RT would explain the increased II\( V_{RT} \) in aMCI \(^+\) but not in AD. In our study of aMCI \(^+\) and CH described earlier, we found that the raised II\( V_{RT} \) in aMCI \(^+\) compared to CH could be accounted for by a slowing in RT\( SPEED \). In the following study we examined whether the increased II\( V_{RT} \) in AD could be accounted for by a slowing in RT\( SPEED \).
Participants
We predicted a significantly greater RT_{SPEED} and IIV_{RT} in AD compared to CH and at levels greater than that seen in aMCI^+, thus a-priori power analysis estimation was based upon one-tailed analysis with an estimated effect size of at least.9, a statistical power level of.8 and a probability level of.05, giving a required minimum total sample group of 32 participants. Community dwelling cognitively healthy older adults (n = 17; 9 males, 8 females) and patients with probable AD (n = 17; 7 males, 10 females) were recruited through the Bristol Memory Disorders Clinic and tested. AD was diagnosed with respect to standard clinical criteria [89] using the same investigations in the previously described study of aMCI^+ patients. The controls were also assessed using this same procedure. Although medication could not be controlled in either group, none of the participants were receiving medication deemed likely to affect cognitive or attention-related function and none of the patients were receiving drug treatment or behavioural intervention for AD at the time of testing. Exclusion criteria included past history of serious head injury, stroke or other significant neurological or psychiatric condition. The task and procedure were identical to those used in the study of the aMCI^+ group. The clinical and demographic details for the CH and AD groups are shown in Table 4. The RT_{SPEED} and IIV_{RT} data for these two groups are shown in Table 5.

Although age did not vary significantly between the two groups \( t (df = 32.6) = .71, p = .49 \), both NART and MMSE were significantly poorer in AD than CH \( t (df = 32) = 3.95, p < .001, \text{ effect size (Cohen's } d) = .95 \) and \( t (df = 32) = 10.17, p < .001, \text{ effect size (Cohen's } d) = 3.5 \) respectively.

Two-tailed analysis revealed that RT_{SPEED} was significantly slower in the group of patients with AD compared to the CH

| Table 4. Clinical and demographic details for the CH and AD groups. |
|------------------------|------------------------|
|                        | CH (n = 17)             | AD (n = 17)             |
| Age                    | 76.7 (5.5)              | 78.4 (7.9)              |
| NART                   | 119.9 (9.3)             | 107.2 (9.6)             |
| MMSE                   | 26.7 (1.7)              | 18.9 (2.7)              |

Mean (SD) age (years), NART (predicted pre-morbid IQ) and MMSE score total score/30 for the CH and AD groups.
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Figure 3. Box plot of the RT_{SPEED} (msec) for the cognitively healthy older adult controls (Old) and patients with aMCI^+ (MCI). doi:10.1371/journal.pone.0065712.g003
Table 5. RT and IIVRT data for each sample group.

| TARGET ALONE | DIFFERENCE |
|--------------|------------|
|               | CH (n=17)  | AD (n=17)  | CH (n=17)  | AD (n=17)  |
| RT speed     | 773.5      | 1748.1     | 910.1      | 231.7      |
| IIVRT (IQR)  | 214.5      | 1147.6     | 1009.7     | 352.9      |
| IIVRT Coef   | 27.4       | 46.7       | 45.6       | 19.7       |
| % errors     | 1.1%       | 7.91%      | -.55%      | -.54%      |

Group mean target alone values and differences [target plus distractors − target alone] for RTSPEED (msec) and mean IIVRT, their corresponding coefficient values and the percentage of excluded trials for the CH and AD groups ([standard deviation in parenthesis]).

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Increasing the Processing Load

For the CH and AD groups, raising the processing load by surrounding the target with distracting information resulted in a significant slowing in RT speed [t (df 16) = 16.18, p < .001] and [t (df 16) = 5.3, p < .001] respectively but RT slowing was significantly greater for the AD compared to the CH group [t (df 16) = 3.84, p < .001, effect size (Cohen's d) = 1.4].

For both CH and AD groups, adding distractors also led to a significant increase in IIVRT [t (df 16) = 11.8, p < .001] and [t (df 16) = 4.7, p < .001] respectively. The magnitude of the increase in IIVRT in response to the distracting information was significantly greater for the AD compared to the CH group [t (df 16) = 3.46, p < .003, effect size (Cohen's d) = 1.2]. Converting IQR to its coefficient value still revealed a significantly greater IIVRT in AD than CH [t (df 16) = 3.8, p < .003] although again, whether error-related RT and IIV was included in analysis or not did not affect study outcome.

Discussion

We investigated the potential influence of RTSPEED, gender, task processing demands, the form of measurement (SD or IQR), and the inclusion or not of error responses, upon the study of IIVRT in aMCI compared to CH. The relationship between RTSPEED and IIVRT in aMCI and AD compared to CH was also investigated. In brief, the unit of measurement for both RTSPEED and IIVRT, and whether error response RTs were included in the analysis or not, failed to alter study outcome. In contrast, gender, processing load and whether RTSPEED was taken into account in the statistical analysis did influence the results. Furthermore, RTSPEED appeared to account for the raised IIVRT in aMCI but not in AD. In the following sections we discuss these findings in greater detail.

Low Task Processing Load Conditions

When the target appeared in isolation, group mean RTSPEED was significantly slowed and IIVRT significantly raised in the both aMCI and AD groups compared to their respective CH control group; an outcome typical of many previous studies [16], [17], [31], [73], [74]. Although no direct statistical comparison was performed, compared to CH, the slowing of RTSPEED was more pronounced in AD, (effect size (Cohen’s d) = 1.62) than in aMCI (effect size (Cohen’s d) = 0.78) and the increase in IIVRT were more pronounced in AD (effect size (Cohen’s d) = 1.3) than in aMCI (effect size (Cohen’s d) = 0.63) compared to CH. This, together with evidence from previous studies [showing that RTSPEED and IIVRT can be preserved in amnestic MCI (aMCI) [e.g.35]] indicates that both measures are sensitive to the degree of cognitive decline, pathological load and neurological dysfunction [34], [90] all of which might be expected to be greater in aMCI than in aMCI, or in the presence of prodromal and frank dementia.

In both the CH and aMCI groups, (for which we had specific neuropsychological test data) neither RTSPEED or IIVRT was significantly correlated with MMSE, NART or neuropsychological (z-score) performance. This may indicate that RTSPEED and IIVRT are influenced by disease-related factors largely independent of those influencing cognitive performance and cognitive reserve and the possibility arises that in aMCI, and indeed in AD, the deficits in IIVRT and RTSPEED occur in parallel to but are not directly related to changes in cognition and underlying cognitive reserve. Alternatively, as our study was not designed primarily to investigate such function with respect to RTSPEED, IIVRT and the coefficient of IIVRT in CH, aMCI and AD, such analysis may be under-powered leading to the expression of a Type II error, rendering further investigation imperative.

As in previous reports e.g. [2] IIVRT was significantly positively correlated with RTSPEED in CH, aMCI and AD. Further analysis using coefficient values of IQR, revealed that IIVRT was no longer significantly increased in aMCI compared to CH when RTSPEED was taken into account, whereas it remained significantly increased in AD compared to CH. These results indicate that the outcome of studies of IIVRT in MCI, i.e., whether IIVRT is significantly different in MCI compared to CH or not, can vary with respect to whether RTSPEED is taken into account in between-group analysis, a finding in accord with several previous studies e.g. [1], [11], [15–17], [19], [31], [38], [65]. As predicted, our results also reveal that although slowed RTSPEED accounts for the greater IIVRT in aMCI compared to CH, it does not account for the significantly raised IIVRT found in AD compared to CH. To speculate, disease burden may be so great in AD compared to aMCI that it actually interferes with or changes processing, rather than simply slowing it. However, as highlighted by one of our anonymous reviewers, it is possible that aMCI and AD differ with respect to whether or not RTSPEED accounts for raised IIVRT as a result of a relative lack of power in one of the studies. Thus future studies, with larger and more similar sample sizes, would more confidently confirm such results.

Furthermore, although there is some evidence from previous studies to suggest that it is IIVRT rather than RTSPEED that better differentiates MCI from CH [12], [15–17], [31], [32] our results reveal a slightly greater effect size when RTSPEED rather than IIVRT is used (Cohen’s d = 0.78) and (Cohen’s d = 0.63) respectively. It is likely therefore study outcome is dependent upon methodology and group demographics and disease factors.
Given the relationship between both slowed RT_{SPEED} and raised IV_{RT} and impaired neurological integrity it is not surprising that IV_{RT} was significantly increased and RT_{SPEED} significantly slowed in aMCI compared to CH. However, to what degree this difference in aMCI can be explained by the presence of prodromal dementia in a proportion of the aMCI group or the result of cognitive change per se remains to be determined using longitudinal methodology. Another point to consider in relation to cognitive function relates to cognitive reserve. In the present study, NART score, (a measure of pre-morbid IQ and one which is often used as a proxy for cognitive reserve), was significantly lower in aMCI compared to CH. This indicates that the patient group may have had lower pre-morbid IQ and thus lower cognitive reserve per se compared to the CH group. It is possible therefore that the significant reduction in RT_{SPEED} and IV_{RT} in aMCI is the result, at least in part, of differences in pre-morbid IQ and cognitive reserve. However, as discussed earlier, this lack of a significant relationship between pre-morbid IQ, NART; cognitive reserve, cognition, MMSE score and RT_{SPEED} and IV_{RT}, may represent the expression of Type II error occurring in the absence of an appropriately powered study designed to look specifically at these factors. Nevertheless, whatever the underlying cause of the difference in IV_{RT} and RT, and whatever the link between MMSE, cognition and pre-morbid IQ or cognitive reserve and IV_{RT} and RT speed and actual brain structure and function, our results indicate a greater degree of disruption to information processing in aMCI than in CH.

Gender

In CH, mean RT_{SPEED} and IV_{RT} did not differ significantly between men and women. In aMCI, RT_{SPEED} was significantly slower, and IV_{RT} significantly greater, in female compared to male patients, although this effect was abolished when RT_{SPEED} was taken into account. The raised IV_{RT} in female patients therefore appeared to be the result of their greater degree of slowing compared to the male patients. Nevertheless, given the relationship between both slowed RT_{SPEED} and raised IV_{RT} and impaired neurological integrity, this finding still indicates a greater degree of neurological dysfunction in the female patients, a finding in support of some neuroimaging and pathological studies e.g. [57], [91], [92]. Furthermore, the significant female-related increase in IV_{RT} and slowing of RT_{SPEED} compared to men seems to be a disease-rather than a normal ageing-related effect. However, some caution in interpreting this outcome is necessary. One should note that within the aMCI group, despite the large effect size (Cohen’s d) of 0.8 for the gender difference in IV_{RT} and the large effect size (Cohen’s d) of 0.7 for the gender difference in RT_{SPEED}, this aspect of the study may have been relatively underpowered as the numbers of males and females within the CH group were relatively low. Clearly therefore further study is required with increased participant numbers. Nevertheless, this preliminary indicator of potentially different gender-related influences upon RT_{SPEED} and IV_{RT} in aMCI and CH indicates (as discussed in the introduction) that it may not be appropriate to assume that in ageing, MCI and AD-related research, any gender effects related to IV_{RT} are similarly expressed in patients and controls.

Although it was not possible to verify the relationship between white matter integrity, cognitive function, pre-morbid IQ; cognitive reserve and IV_{RT} and RT function in the present study, the female patients with aMCI appeared able to perform at a similar cognitive level as male patients despite evidence from RT_{SPEED} and IV_{RT} measures of a greater underlying neurological dysfunction. One could argue therefore that this provides evidence for a greater degree of cognitive reserve in female compared to male patients, (a finding in accord with some previous studies). Although our NART proxy measure of cognitive reserve does not support this hypothesis, it is possible that this results from the fact that our study was not specifically designed, and thus powered, to study gender-related cognitive reserve as measured by NART proxy. Clearly, however, the evidence for such gender-related discrepancy indicates that further research is required in order to determine the relationship between white matter integrity, IV_{RT} and RT function, cognitive performance and cognitive reserve and gender.

In view of evidence showing that for MCI the risk of progression to dementia is greater in females than males and that females may progress more rapidly through the transition phase to AD [42], it is also possible that IV_{RT} was greater in female than male aMCI patients in our study because they were more likely to have prodromal dementia, or simply at a later disease stage, despite our gender-matching on behavioural measures of cognitive function, MMSE, diagnosis and stage. In the absence of longitudinal follow up, this possibility cannot be determined in the present study. Nevertheless, irrespective of causality, our results indicate that in patients newly diagnosed with aMCI (as were ours), females can exhibit a similar cognitive and diagnostic profile to men but in fact be suffering considerably worse neurological disruption, which although not ostensibly affecting clinical measures of cognition, may have a detrimental impact upon other aspects of brain processing and thus behaviour. This may be particularly important when one considers the evidence to suggest that those with greater reserve are less amenable to early detection using cognitive measures [93]. However, one must apply some caution to such speculation until studies with greater numbers of male and female participants can be performed.

Our results provide additional evidence to support the consideration of gender stratification in research and in the interpretation of results in clinical practice. The importance of considering the influence of gender upon study outcome when investigating RT_{SPEED} and IV_{RT} in MCI and AD compared to CH is also confirmed by these results.

Increasing the Processing Load

As expected, raising the processing load by surrounding the target with distracting information slowed mean RT_{SPEED} and raised IV_{RT} compared to that evoked by the low processing load task in CH, aMCI and AD, with the effect being significantly greater in both patient groups compared to CH. This indicates that task variation, particularly in processing load, may be a factor to consider when examining outcome variation in such studies.

When RT_{SPEED} was taken into account the significantly greater IV_{RT} in aMCI compared to CH was abolished, thus indicating that, as in the case for the low processing load condition, raised IV_{RT} in aMCI compared to CH can be explained by their slowed RT_{SPEED}. In contrast, when RT_{SPEED} was taken into account in the comparison of IV_{RT} in AD compared to CH under high processing load conditions the significantly greater IV_{RT} in AD was replaced by a significantly greater IV_{RT} in CH compared to AD. This indicates that RT_{SPEED} explains the greater IV_{RT} in AD compared to CH under high processing load conditions and that, in CH, raising the processing load can increase IV_{RT} independently of RT_{SPEED}. These results indicate once again that whether or not RT_{SPEED} is taken into account in IV_{RT} analysis can affect study outcome and that this effect can vary with respect to the groups investigated and the processing demands of the task.
Raising the processing load increased the group difference in $RT_{\text{SPEED}}$ between aMCI$^+$ and CH (from effect size, Cohen's $d = .78$ to .9) and reduced the comparison of $RT_{\text{SPEED}}$ between AD and CH (from effect size, Cohen's $d = 1.62$ to 1.4). For IVRT, increasing the processing load resulted in a reduction in the effect size from .70 to aMCI$^+$ and CH (from effect size, Cohen's $d = .63$ to .52) compared to the low processing load condition and also only slightly reduced the differentiation in IVRT between AD and CH (from effect, Cohen's $d = 1.3$ to 1.2). Therefore increasing the processing load of a task per se does not necessarily increase group differentiation in the study of MCI and AD, appearing instead to be determined by factors such as what is being measured (e.g. $RT_{\text{SPEED}}$ or IVRT), the group under study and indeed whether or not $RT_{\text{SPEED}}$ is taken into account in IVRT analysis.

In CH, the absence of gender related influences upon $RT_{\text{SPEED}}$ and IVRT in the low-processing load condition was maintained when processing load increased. However, in the aMCI$^+$ group, the slower $RT_{\text{SPEED}}$ and greater IVRT for female compared to male patients in the low processing load condition were abolished with the increase in processing load. Thus gender effects also appear contingent upon the task employed. Although we were unable to examine gender-related effects in our AD group the possibility arises that gender may also influence research in this group of people.

**Study Limitations**

As already highlighted, it is possible that in our study of IVRT and $RT_{\text{SPEED}}$ in aMCI$^+$ compared to CH, outcome was affected by the proportion of aMCI$^+$ patients with pro-dromal dementia. In the absence of longitudinal analysis, we cannot determine whether, for example, this affects the magnitude of the effect between CH and aMCI$^+$ per se and especially whether the significantly greater IVRT and $RT_{\text{SPEED}}$ for female compared to male patients may be simply a result of the fact that a greater proportion of females had pro-dromal dementia. The lack of white matter analysis (e.g. DTI) or other functional/anatomical imaging techniques also precluded the investigation of the relationship between structural and functional brain changes, IVRT, $RT_{\text{SPEED}}$, cognition, cognitive reserve and gender. In the study of $RT_{\text{SPEED}}$ and IVRT there are many factors in addition to the ones investigated here, potentially capable of influencing both the speed and variability of processing in ageing, aMCI$^+$ and AD and thus warrant further investigation. Such factors include fatigue and practice effects, stimulus characteristics, sensory-motor integration, decision and response and temporal factors, e.g. [94]. Finally, a larger sample size would more confidently confirm differences and would have permitted also the potentially more clinically appropriate comparison of female patients with female controls and male patients with male controls.

**Summary**

We have shown that in the study of IVRT in CH, MCI and AD, study outcome is prone to influence by a variety of factors acting independently and possibly interactively. This evidence of raised IVRT and slowed $RT_{\text{SPEED}}$ also indicates that information processing in MCI and AD may be more compromised than revealed by routine neuropsychological testing and so may impact upon daily behaviours which depend upon $RT_{\text{SPEED}}$ and consistency of processing, such as driving and avoidance of falls.

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**Author Contributions**

Conceived and designed the experiments: AT MP PR JH AB. Performed the experiments: AT MP PR JH AB. Analyzed the data: AT. Wrote the paper: AT MP PR JH AB.

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