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Reaction Time and Visible White Matter Lesions in Subcortical Ischemic Vascular Cognitive Impairment

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Abstract. Slowed behavioral reaction time is associated with pathological brain changes, including white matter lesions, the common clinical characteristic of subcortical ischemic vascular cognitive impairment (SIVCI). In the present study, reaction time (RT) employing Trails B of the Trail Making Test, with responses capped at 300 s, was investigated in SIVCI ($n=27$) compared to cognitively healthy aging (CH) ($n=26$). RT was significantly slowed in SIVCI compared to CH (Cohen's d effect size = 1.26). Furthermore, failure to complete Trails B within 300 s was also a characteristic of SIVCI although some ostensibly cognitively healthy older adults also failed to complete within this time limit. Within the SIVCI group, RT did not differ significantly with respect to whether the patients were classified as having moderate/severe or mild, periventricular white matter changes visible on their diagnostic CT/MRI scans. This, together with the high degree of overlap in RT between the two SIVCI subgroups, raises the possibility that using visible ratings scales in isolation may lead to the underestimation of disease level.

Keywords: Methodology, reaction time, subcortical ischemic vascular cognitive impairment, Trail Making Test

INTRODUCTION

Clinically, subcortical ischemic vascular cognitive impairment (SIVCI) is characterized by periventricular white matter changes (leukoaraiosis [LA]) [1–4]. Nevertheless, it can be difficult to determine the clinical extent and relevance of white matter lesions in SIVCI particularly as their full extent may not be visible on diagnostic CT/MRI scans. In the research domain, a significant body of evidence supports a strong association between pathological brain

changes, including distributed or global structural and functional breakdown in white matter, and cognitive decline [5–13], particularly behavioral reaction time (RT) [6–10, 14–25]. Testing RT may therefore be an important adjunct to the diagnosis of SIVCI and the determination of disease load that may not be fully represented by the level of periventricular white matter visible on diagnostic scans. Evidence is however lacking with respect to which RT tests may be most sensitive to SIVCI. Furthermore, in principle, examining RT using a variety of tests (whose varying designs and performance requirements can be expected to recruit different processing networks, at least in part) may improve the identification of slowing in various aspects of behaviour relevant to every-

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day function in individuals living with SIVCI. To address this issue, we examined RT using two tests in the same patient and cognitively healthy (CH) control groups.

In the first part of this study [26], RT was examined using a multi-trial, computer-based visual search test, typically used in research. Participants were instructed to respond to whether a pre-defined target was pointing to the left or right, when it appeared in isolation and when it was surrounded by distracting stimuli. RT was significantly slower in SIVCI compared to CH under both conditions, but particularly slow in the presence of distracting information¹ (Cohen's effect size 1.19). Within the SIVCI group, RT did not however vary significantly with respect to whether the level of periventricular LA (based on the Age-Related White Matter Changes Rating Scale (ARWMC) [27]) was mild or moderate/severe. This lack of significance could be the consequence of relatively low numbers of patients within each subgroup (mild, $n = 15$, versus moderate/severe, $n = 12$). Nevertheless, there was a high degree of variability in RT within each subgroup, i.e., in those ostensibly with the same level of disease, and substantial overlap in RT between patients classified as having mild and moderate/severe levels of disease. This raises the possibility that the level of CT- or MRI-visible periventricular white matter change alone does not fully explain the highly significant RT slowing in SIVCI compared to CH. RT results may also represent the impact of 'silent' white matter disease and/or other disease related changes in SIVCI. It is also possible that a different test of RT may be more representative of visible periventricular white matter changes in SIVCI.

In this study, we examine RT using Trails B of the Trail Making Test (TMT) [28, 29] in the same participants who took part in the visual search RT study [26]. Trails B was examined because it represents a typical clinical test of RT and we wanted to examine whether it provided RT results comparable to those resulting from the use of a research-based test of such function. Given that multiple processes underlie both visual search and TMT (which also requires a serial search strategy), it is likely that both tests recruit a network of interconnected regions rather than single brain regions, some of which will be recruited by both tests. One can therefore expect some overlap in RT performance. Nevertheless, there are differences with

respect to factors such as processing demands, stimulus processing, motor and oculomotor components, performance strategies, and the number of trials presented [30–33]. Such differences can be expected, at least in part, to lead to the recruitment of different processing networks and thus potentially differential sensitivity to the presence of disease.

Trails B lacks some of the benefits of the visual search test [34] and can be difficult to perform, particularly for those from clinical populations [15, 34–36]. Nevertheless, like the visual search test, performance recruits distributed aspects of information processing and thus can be highly sensitive to neurological impairment [29]. Furthermore, in contrast to the visual search task, Trails B is already widely used in clinical practice and research and does not require a computer for administration.

METHODS

Ethical approval

Ethical approval was granted by the NHS Health and Research Authority Wales Research Ethics Committee 6, and Research and Development, Cardiff and Vale NHS Trust. Only participants who had the capacity to make an informed decision were included in the study (according to The Mental Capacity Act 2005/2019: Health Research Authority). All participants gave written informed consent.

Participants

On an incident patient basis, 27 patients with SIVCI were recruited via their referral to the Memory Clinic at Llandough Hospital, Cardiff, Wales, UK. They were diagnosed with minor or major neurocognitive disorder associated with lacunar infarcts and ischemic white matter lesions (LA), located predominantly subcortically [3, 37]. In accord with normal clinical practice, diagnosis included neuroimaging (typically CT scans, or MRI scans if requested) from which the extent of periventricular LA was assessed using the ARWMC Scale [27], detailed clinical history, routine laboratory tests and a neuropsychological test battery including, Addenbrooke's Cognitive Examination III [37], the Montreal Cognitive Assessment (MoCA) [38], Test of Premorbid Functioning [39], National Adult Reading Test [40], and the Hospital Anxiety and Depression Scale [41]. Inclusion criteria included

¹A high processing load condition designed to evoke a search strategy involving serial attentional disengagement, shifting and engagement throughout the stimuli until the target is found.

capacity to provide informed consent (as assessed by clinicians according to The Mental Capacity act 2005/2019: Health Research Authority), mild to moderate cognitive impairment (MoCA score between 12 and 25 and/or Addenbrooke's Cognitive Examination III score between 50 and 90), normal or corrected-to-normal vision and hearing, and physical ability to perform the research tasks. Exclusion criteria included other significant contributory cause of cognitive impairment (e.g., clinically significant neurological, psychiatric, psychological or medical conditions), use of psychoactive drugs (at present or a history thereof) of substance or alcohol dependency, and problems with motor or manual dexterity.

The CH group ($n=26$) were recruited from relatives of patients attending the Llandough Memory Clinic who were participating in this study, research volunteers from the Centre for Ageing and Dementia Research (CADR) and the older adult research volunteer database at Swansea University. Inclusion criteria included MoCA scores of >25 , normal or corrected-to-normal vision and hearing, and the physical ability to perform the research tasks. Exclusion criteria included self-reported cognitive change or impairment, or visits to their general practitioner or memory services regarding concerns about such function, significant neurological, psychiatric, or medical condition, psychoactive drug use, and current or a history of substance or alcohol dependency. The use of prescribed and non-prescribed medication was recorded but not controlled.

Within the SIVCI group, CT or MRI scan-visible periventricular white matter change was assessed using the ARWMC scale [27], with 0 = no lesions, 1 = focal lesions, 2 = beginning of lesion confluence, 3 = diffuse involvement of the entire region. Fifteen patients were diagnosed with mild (ARWMC score of 0 or 1), and 12 were diagnosed with moderate to severe (ARWMC score of 2 or 3), visible periventricular white matter change. Assessment was undertaken by two experienced professionals in the field (AB and AT) who independently rated each scan, yielding a 93% (25 out of the 27 scans) consensus rate. The remaining two scores were agreed by consensus after discussion.

The Trail Making Test

Trails B of the TMT [28, 29], was administered according to standard administration instructions [29]. RT was indicated by the time taken to complete the test (with the time taken to self-correct any

error included in the score), with a performance time limit of 300 s in accordance with typical clinical time limits [29]. Participants were provided with the standard practice trial. Performance feedback was not provided.

Data analysis

The data from individuals who failed to complete Trails B within 300 s were included in the statistical analysis, but RT was capped at 300 s [29]. As the RT data was generally normally distributed, with variance similar for both groups, parametric analysis was employed. Note, however, that in light of the significant polemic surrounding the issues of statistical analysis in RT research, the data were also analyzed using non-parametric tests. The results of these tests were the same as those using the parametric tests and thus are not described here.

RESULTS

Demographics

The demographic details are displayed in Table 1.

Independent samples *t*-test analysis revealed no significant differences in mean age, anxiety, or depression scores between the CH and SIVCI groups [all p -values >0.05]. Mean educational level was however significantly lower for the SIVCI compared to the CH group [$t(44.72) = 3.7, p = 0.001$, two tailed, $d = 1.005$, 95% CI (1.5, 5.21)].

Reaction time

The group mean RT scores are displayed in Table 2.

Table 1
Group mean demographic details for the CH and the SIVCI patient groups. Standard deviation in parenthesis

	CH	SIVCI	Difference in mean values (CH – SIVCI)
Total N	26	27	
Age mean (y)	76.19 (5.51)	78.11 (6.14)	-1.92
Age range	70–86	68–91	
Gender (N)	26.9% Male, 73.1% Female	51.9% Male, 48.1% Female	
Years in full time education	15.69 (3.87)	12.33 (2.72)	3.36
Educational range	10–22	8–21	
MoCA score	28.12 (1.42)	19.93 (3.28)	8.19
Anxiety	5.7 (3.8)	6.08 (3.68)	-0.38
Depression	2.9 (2.86)	4.29 (3.43)	-1.39

Table 2
Group mean RT (in seconds; standard deviation in parenthesis) for Trails B

	RT CH (<i>n</i> = 26)	RT SIVCI (<i>n</i> = 27)	Difference in means (CH – SIVCI)
Trails B	135.81 (103.1)	255.38 (85.8)	-119.57

Previous reports that Trails B can be a particularly difficult task to perform, especially for those from clinical populations [15–18], are supported by the results of the present study as 25.9% of the CH and 73.1% of the SIVCI groups failed to complete within 300 s. To overcome this issue, participants who failed to complete within this time limit were included but their data was capped at the maximum 300 s.

For Trails B, independent *t*-test analysis revealed that RT was again significantly slower for the SIVCI compared to the CH group [$t(51) = -4.6$, $p < 0.001$, Effect size, Cohen's $d = 1.26$, 95% CI (-171.8, -67.35)]. There was no significant correlation between Trails B RT and educational level for either the CH [$r = 0.056$, $p = 0.79$] or SIVCI group, [$r = 0.26$, $p = 0.19$] and the results did not vary significantly with respect to gender [all p -values > 0.05].

Reaction time and level of white matter change in SIVCI

Group mean level (mild or moderate/severe) of visible periventricular white matter lesions and Reaction time (s) for the SIVCI group is displayed in Table 3.

Ten out of the fifteen patients (66.7%) with a mild level of white matter disease, and ten out of the twelve patients (83.3%) with a moderate/severe level of white matter disease failed to complete Trails B within the 300 s time limit.

The mean RT for the moderate/severe group was approximately 33 s slower than that for the mild group, but this difference failed to reach significance [$p > 0.05$].

Table 3
Mean level (mild or moderate/severe) of visible periventricular white matter lesions and Reaction time (seconds) for the SIVCI group. Standard deviation in parenthesis

Mean level of white matter disease	Number of participants	Trails B Mean RT
Mild 0.6 (0.51)	15	240.39 (100.78)
Moderate/severe 2.42 (0.52)	12	274.12 (61.5)

DISCUSSION

Reaction time in SIVCI compared to CH

In a recent study [26], we examined RT in SIVCI using a multi-trial, computer-based visual search test. Although this test revealed significantly slower RT in SIVCI compared to CH, RT did not vary significantly with respect to whether the level of periventricular white matter change in SIVCI was mild or moderate/severe [27]. We [26] suggested this lack of significance could be the consequence of relatively low numbers of patients within each subgroup (mild, $n = 15$, versus moderate/severe, $n = 12$). There was, however, a high degree of variability in RT within each subgroup, i.e., in those ostensibly with the same disease level, together with considerable RT overlap between those classified as having mild and moderate/severe levels of disease. This suggests that the level of CT- or MRI-visible periventricular white matter change alone might not fully explain the highly significant slowing of RT in SIVCI compared to CH, as RT slowing may also represent the impact of 'silent' white matter disease and/or other disease related changes in SIVCI [6–10, 14–25]. It is also possible that the results from different RT tests may be more closely associated with visible periventricular white matter changes in SIVCI. The aim of this study was therefore to examine RT using Trails B of the TMT, to measure RT in SIVCI compared to CH in the same individuals taking the visual search test.

Trails B revealed a significantly slowed RT in SIVCI compared to CH, with a Cohen's effect size of 1.26. It is clear that for the same participants, Trails B RT appears similarly sensitive to that evoked by the visual search test, particularly when the target was surrounded by distracting information, which resulted in a Cohen's effect size of 1.19 [26]. Both tests therefore provide robust evidence of significant RT slowing in SIVCI compared to CH. The similarity of results suggests that both the Trails B test and the visual search test used in our previous study [26] share some common information processing networks, and/or that pathological change is so widespread that many tests of RT (which is also a distributed network function) will show a similar degree of abnormality in SIVCI.

Level of completion for Trails B

In the present study, 25.9% of CH older adults and of 73.1% of patients with SIVCI failed to complete

Trails B within the 300 s time limit. Furthermore, within the SIVCI group, ten out of fifteen patients (66.7%) with mild white matter disease, and ten out of the twelve patients (83.3%) with moderate/severe levels, failed to complete in time.

To overcome this issue, the RT of participants who failed to complete were included but capped at the maximum 300 s. Arguably, imposing such a time limit may mask the 'true' extent of slowing. However, this has to be considered alongside the possibility that allowing any longer for completion invokes a greater likelihood of effects such as lack of concentration. Nevertheless, despite this time limit, RT was still significantly slowed in SIVCI compared to CH. Furthermore, in accordance with findings from other studies, our results indicate that failure to complete Trails B in time *per se* is indicative of disease [16–18], specifically for SIVCI in this study. Our results are more surprising with respect to the performance of the CH group, with approximately 25% failing to complete Trails B in time. Unfortunately, we could not obtain CT/MRI scans for the CH group. Although white matter disease is a feature of cognitively healthy aging, it is possible that those who failed to complete in time were not as 'cognitively healthy' as their results of the neuropsychological tests used in our study would suggest. Despite this potential overlap in higher RTs with some individuals within the SIVCI group, RT was still significantly slower in SIVCI compared to CH.

The relationship between the level of visible periventricular white matter change and RT in SIVCI

In our previous study [26], there was no significant difference in visual search-related RT between the mild versus moderate/severe white matter change subgroups of the SIVCI group. We argued that a possible contributory factor was the test used to measure RT. However, the present study reveals that Trails B RT also did not vary significantly between the SIVCI subgroups. These results provide further support for the suggestion that the level of periventricular white matter disease visible on typical CT and MRI scans may not fully represent the level of pathology in SIVCI. However, such speculation has to be tempered again by the relatively low numbers of participants in this study (the result of known difficulties in recruiting patients with this strict SIVCI diagnosis) and in particular the relatively low numbers of patients within each SIVCI subgroup. Nevertheless,

the high degree of within-group variability in RT, in both groups but particularly the mild group, and the substantial overlap in RT between groups with ostensibly different levels of periventricular white matter changes (see Table 3) provides some indication that CT/MRI-visible levels of periventricular white matter changes alone do not fully account for the RT results.

Potential study limitations and future research

Potential study limitations include the aforementioned relatively low participant numbers within the SIVCI subgroups with respect to determining the relationship between periventricular white matter change and RT (although the effect sizes for the RT were high and indicative of an appropriately powered study for the measurement of RT *per se* in SIVCI). The relatively low patient numbers reflect the difficulty in recruiting participants with respect to the inclusion and exclusion criteria necessary for the inclusion of individuals with strictly defined SIVCI [4]. In addition, we were unable to perform CT/MRI scans for the CH control group, and also were unable to perform DTI scans for either group. This precluded the ability to examine the relationship between global measure of white matter integrity (and other pathological changes) and RT. Examination of the specific networks recruited by Trails B and the visual search test and any pathological change affecting these networks was also not possible.

In terms of future studies, we suggest a repeat of the current study with greater participant numbers and a wider range of RT tests and with a significant neuroimaging component with longitudinal assessment, including voxel-based morphometry to assess grey matter volume change, diffusion-weighted imaging of white matter integrity (especially markers of demyelination), and the performance of RT tests during fMRI and resting state, in order to gain evidence of any relationship between RT and structural and functional changes over time.

Conclusion

In the present study, it was not possible to provide independent evidence of the well-established relationship between white matter integrity and behavioral RT [5–25]; it is possible however, that slowing in SIVCI may also reflect 'silent' white matter changes and the presence of other pathological changes such as demyelination, atrophy, micro-infarcts, grey matter, and neurochemical changes

[42]. Although research with greater participant numbers within SIVCI subgroups is required, it is possible that interpreting CT/MRI-visible ratings of periventricular white matter changes in isolation may lead to the underestimation of disease burden *per se*, and an underestimation of its variability within individuals classified as having the same level of disease.

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