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-
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

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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                                   | –1.92 |
| Age mean (y) | 76.19 (5.51)                                                                                | 78.11 (6.14)                         | –2.92 |
| Age range | 70–86                                                                                           | 68–91                                | –2.00 |
| Gender (N) | 26.9% Male, 51.9% Male, 73.1% Female                                                            | 48.1% Female                         | –3.20 |
| Years in full time education | 15.69 (3.87)                                                                                | 12.33 (2.72)                         | 3.36 |
| Educational range | 10–22                                                                                           | 8–21                                 | –4.00 |
| 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 |
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].

### 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

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**Table 2**

| Group | Mean RT (in seconds; standard deviation in parenthesis) for Trails B | Difference in means (CH – SIVCI) |
|-------|-----------------------------------------------------------------|----------------------------------|
| CH    | (n = 26) 135.81 (103.1)                                       | 255.38 (85.8) –119.57            |

**Table 3**

| 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)             |
 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, microinfarcts, grey matter, and neurochemical changes.
[42]. Although research with greater participant numbers within SIVC1 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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REFERENCES

[1] Smith EE (2017) Clinical presentation and epidemiology of vascular dementia. Clin Sci 131, 1059-1068.
[2] Dichgans M, Leys D (2017) Vascular cognitive impairment. Circ Res 120, 573-591.
[3] Wallin A, Román GC, Esiri M, Kettunen P, Svensson J, Parasekvas GP, Kapaki E (2018) Update on vascular cognitive impairment associated with subcortical small-vessel disease. J Alzheimers Dis 62, 1417-1441.
[4] Skrobot OA, Black SE, Chen C, De Carli C, Erkinjuntti T, Ford GA, Kalaria RN, O’Brien J, Pantoni L, Pasquier F, Roman GC, Wallin A, Sachdev P, Skoog I, Ben-Shlomo Y, Passmore AP, Love S, Kehoe PG (2017) Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the vascular impairment of cognition classification study. Alzheimers Dement 14, 1-13.
[5] Wiggins MW, Tannen J, Schwab N, Crowly SJ, Schmallfus I, Brumbach B, Liban D, Heilman K, Price CC (2019) Regional leukoaraiosis and cognition in non-demented older adults. Brain Imaging Behav 13, 1246-1254.
[6] Heinen R, Vlegels N, de Bresser J, Leemans A, Biessels GJ, Reijmer YD (2018) The cumulative effect of small vessel disease lesions is reflected in structural brain networks of memory clinic patients. Neuroimage Clin 19, 963-969.
[7] Claus JJ, Coenan M, Skaebenborg SS, Schuur J, Tielkes CEM, Koster P, Scheltens P (2018) Cerebral white matter lesions have low impact on cognitive function in a large elderly memory clinic population. J Alzheimers Dis 63, 1129-1139.
[8] Cremers LGM, de Groot M, Hofman A, Krestin GP, van der Lugt A, Niessen WJ, Vernooij MW, Ikrar MA (2016) Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study. Neurobiol Aging 39, 108-117.
[9] Biesbroek JM, Weaver NA, Hilal S, Kuijf HJ, Ikrar MK, Xu X, Tan By, Venktasubramanian N, Postma A, Biessels GJ, Chen CP (2016) Impact of strategically located white matter hyperintensities on cognition in memory clinic patients with small vessel disease. PLoS One 11, e0166261.
[10] Prins ND, Scheltens P (2015) White matter hyperintensities, cognitive impairment and dementia: An update. Nat Rev Neurol 11, 157-165.
[11] Vasquez BP, Zakianes KK (2015) The neuropsychological profile of vascular cognitive impairment not demented: A meta-analysis. J Neuropsychol 9, 109-136.
[12] Ramirez J, McNeely AA, Scott CJM, Stuss DT, Black SE (2014) Subcortical hyperintensity volumetrics in Alzheimer’s disease and normal elderly in the Sunnybrook Dementia Study: Correlations with atrophy, executive function, mental processing, speed and verbal memory. Alzheimers Res Ther 6, 49.
[13] Sudo FK, Alves CEO, Ericeira-Valente L, Tiel C, Moreira DM, Laks J, Engelhardt E (2013) White matter hyperintensities, executive function and global cognitive performance in vascular mild cognitive impairment. Arq Neuropsiquiatr 7, 431-436.
[14] Yang Y, Bender AR, Raz N (2015) Age related differences in reaction time components and diffusion properties of normal-appearing white matter in healthy adults. Neuropsychologia 66, 246-258.
[15] MacPherson SE, Cox SR, Dickie DA, Karama S, Starr JM, Evans AC, Bastin ME, Wardlaw JM, Deary IJ (2017) Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. Cortex 95, 92-103.
[16] Biesbroek JM, Kuijf HJ, van der Graaf Y, Vincken KI, Postma A, Mali WP, Biessels GJ, Geerlings MI (2013) Association between subcortical vascular lesion location and cognition: A voxel-based and tract-based lesion-symptom mapping study. The SMART-MR study. PLoS One 8, e60541.
[17] Kuznetsova KA, Maniega SM, Ritchie SJ, Cox SR, Storkey AJ, Starr JM, Wardlaw JM, Deary IJ, Bastin ME (2016) Brain white matter structure and information processing speed in healthy older age. Brain Struct Funct 221, 3223-3235.
[18] Jouvant E, Reyes S, De Guio F, Chabriat H (2015) Reaction time is a marker of early cognitive and behavioral alterations in pure cerebral small vessel disease. J Alzheimers Dis 47, 413-419.
[19] Duering M, Gonik M, Malik R, Zieren N, Reyes S, Jouvent E, Hervé D, Gschwendtner A, Opherk C, Chabriat H, Dichgans M (2013) Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. Neuroimage 66, 177-183.
[20] Jacobs HIL, Leritz EC, Williams VJ, van Boxtel MPJ, van der Elst W, Jolles J (2013) Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. Hum Brain Mapp 34, 77-95.
[21] Lu PH, Lee GL, Tishler TA, Meghpara M, Thompson PM, Bartzokis G (2013) Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men. Brain Cogn 81, 131-138.
[22] Kerchner GA, Racine CA, Hale S, Wilheim R, Laluz V, Miller BL, Kramer JH (2012) Cognitive processing speed in older adults: Relationship with white matter integrity. PLoS One 7, e50425.
[23] Nilsson J, Thomas AJ, O’Brien JT, Gallagher P (2014) White matter and cognitive decline in aging: A focus on processing speed and variability. J Int Neuropsychol Soc 20, 262-267.
[25] Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, Jack CR, Weiner M, DeCarli C (2010) Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol* 67, 1370-1378.

[26] Richards E, Bayer A, Tree JJ, Hanley C, Norris JE, Tales A (2019) Subcortical ischemic vascular cognitive impairment: Insight from reaction time measures. *J Alzheimers Dis* 72, 845-857.

[27] Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren A, Wallin A, Ader H, Leys D, Panto li L, Pasquier F, Erkinjuntti T, Scheltens P (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 32, 1318-1322.

[28] Reitan RM, Wolfson D (2004) The Trail Making Test as an initial screening procedure for neuropsychological impairment in older children. *Arch Clin Neuropsychol* 19, 281-288.

[29] Bowie CR, Harvey PD (2006) Administration and interpretation of the Trail making Test. *Nat Protoc* 5, 2277-2281.

[30] Varjacic A, Mantini D, Demeyere N, Gillebert CR (2018) Neural signatures of Trail Making Test performance: Evidence from lesion-mapping and neuroimaging studies. *Neuropsychologia* 115, 78-87.

[31] Fairhill SL, Indovina I, Driver J, Macaluso E (2009) The brain network underlying serial visual search: Comparing overt and covert spatial orienting, for activations and for effective connectivity. *Cereb Cortex* 19, 2946-2958.

[32] Gitelman DR, Parrish TB, Friston KJ, Mesulam M-M (2002) Functional anatomy of visual search: Regional segregations within the frontal eye fields and effective connectivity of the superior colliculus. *Neuroimage* 15, 970-982.

[33] Peelan MV, Kastner S (2011) A neural basis for real-world visual search in human occipitotemporal cortex. *Proc Natl Acad Sci U S A* 108, 12125-12130.

[34] Haworth J, Phillips M, Newson M, Rogers P, Torres-Burton A, Tales A (2016) Measuring information processing speed in mild cognitive impairment: Clinical versus research dichotomy. *J Alzheimers Dis* 51, 263-275.

[35] Oosterman JM, Vogels RLC, van Harten B, Gouw AA, Poggesi A, Scheltens P, Kessels RP, Scherder EJ (2010) Assessing mental flexibility: Neuroanatomical and neuropsychological correlates of the trail making test in elderly people. *Clin Neuropsychol* 2, 203-219.

[36] Chan E, MacPherson SE, Robinson G, Turner M, Lecce F, Shallice T, Cipolotti L (2015) Limitations of the Trail making Test-B in assessing frontal executive dysfunction. *J Int Neuropsychol Soc* 2, 169-174.

[37] Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR (2013) Validation of the Addenbrooke’s Cognitive Examination III in frontotemporal dementia and Alzheimer’s disease. *Dement Geriatr Cogn Disord* 36, 242-250.

[38] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53, 695-699.

[39] Wechsler D (2011) *The Test of Premorbid Functioning –UK Version (TOPF UK) Manual*. Psychological Corporation, San Antonio, TX.

[40] Nelson H, Willison J (1991) *National Adult Reading Test (NART)*. Test manual including new data supplement. NFER-Nelson, Windsor.

[41] Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 67, 361-370.

[42] Kalaria RN (2016) Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer’s disease. *Acta Neuropathol* 131, 659-685.