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Inhibitory control deficits in vascular cognitive impairment revealed using the MILO task.

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Keywords

VCI (vascular cognitive impairment), MILO (Multi-Item Localisation) task, dementia, reaction time, inhibitory control, Visual search, Attention, Ageing

Abstract

We used the MILO (Multi-Item Localization) task to characterise the performance of a group of older adults diagnosed with mild to moderate vascular cognitive impairment (VCI). The MILO task is designed to explore the temporal context of visual search and in addition to measuring overall completion time, provides a profile of serial reaction time (SRT) patterns across all items in a sequence. Of particular interest here is the Vanish/Remain MILO manipulation that can identify problems with inhibitory control during search. Typically, SRT functions closely overlap, regardless of whether items Vanish or Remain visible when selected, indicating an ability to ignore previously selected targets. Based on the distributed nature of VCI-related pathology and previous visual search studies from our group, we speculated that MILO performance would be compromised in this group of participants when items remained visible after being selected relative to when they vanished. Compared to cognitively healthy, age-matched control participants, the performance of VCI participants was characterised by overall slowing, increased error rates, and crucially, a compromised ability to ignore past locations. As predicted, the Vanish versus Remain SRT functions of VCI participants significantly diverged towards the end of the sequence, which was not the case for control groups. Overall, our findings suggest that the MILO task could be a useful tool for identifying non-age-related changes in behaviour with patient populations, and more generally hints at a possible inhibitory deficit in VCI.

Introduction

White matter changes visible on neuroimaging are characteristics of vascular cognitive impairment (VCI; Dichgans et al 2017; Wallin et al 2018; Skrobot et al 2017; Wiggins et al 2019; Heinen et al 2018; Clauss et al 2018; Cremers et al 2016). Behaviourally, VCI is known to give rise to deficits in a range of attention-related, inhibitory control and cognitive functions (Pantsiou et al 2018, Dichgans and Leys 2017, Vasquez and Zakzanis 2015, Wallin et al 2018), often indexed with the use of reaction time (RT) measures. More generally, as reaction time (RT) and its intra-individual variability (IIV) are known behavioural markers of the functional integrity of white matter (Yang et al 2015; MacPherson et al 2017; Kuznetsova et al 2016; Jouvant et al 2015; Duering et al 2013; Jacobs et al 2013), one would expect to see disproportionate slowing and raised IIV in VCI compared to cognitively healthy ageing, and indeed such a pattern has been reported (Richards et al., 2019a,b; de Jager 2004; Cohen et al., 2002). RT is particularly slowed when assessed using tests of executive function (Richards et al., 2019a,b; de Jager 2004) a finding probably related to the distributed nature of VCI-related pathology.

Assessment tools, such as the well-known Trail Making Test (TMT; Reitan, 1958; Salthouse, 2011; Rabin et al., 2007; Lange et al., 2005; Bowie & Harvey, 2006) -- often used clinically to measure executive function-related information processing speed -- typically consider RT only in terms of overall completion time. Doing so limits the ability to reveal the integrity of specific functional subcomponents of information processing related to RT that are affected by VCI, thus also limiting our understanding of behavioural change, signs and symptoms, disease progression (de Groot et al 2000; Sudo et al 2017) and the potential for intervention. The increasing evidence that pathological changes in white matter can be 'silent', i.e., not visible on routine neuroimaging, together with the fact that not all tests used clinically may be sensitive to such effects, highlights the importance of using of a wider range of tests than may be used at present in both clinical and research arenas. Failure to consider the brain/behaviour relationship may mean that the effects of VCI are underestimated.

The purpose of the current paper was to further our understanding of the behavioural consequences of white matter changes in VCI by using a task that does have the potential to reveal the integrity of specific functional subcomponents as well as overall RT. A previous study from our group examined visual search in VCI, and revealed that distracting information within the visual environment has a significantly greater detrimental effect upon performance

in VCI compared to cognitively healthy older adults (Richards et al 2019a). Extending this line of work, here we report an initial set of findings from a study in which we used the search-related MILO (Multi-Item Localisation) task (Thornton and Horowitz 2004; 2020a,b; Horowitz & Thornton, 2008) to assess the performance of a group of older adults diagnosed with mild to moderate VCI.

As described in more detail below, the MILO task requires participants to quickly search and respond to a sequence of target items. Such sequential search is thought to engage a broad set of cognitive and attention-related operations, and thus has the potential to reveal subtle deficits that may be masked in standard tests of RT. Specifically, in addition to measuring overall completion time (i.e. RT) and error rates, the MILO task makes it possible to separately assess potential deficits in both anticipatory planning and inhibitory control. In the following sections, we first briefly introduce the MILO task and relevant previous findings before describing the current experimental design and presenting our results.

The MILO Task

The MILO task was originally developed as a basic research tool for exploring the temporal context of visual search (Horowitz & Thornton, 2008; Thornton & Horowitz, 2004). In contrast to the standard visual search tasks -- which typically involve detecting a single target amongst a variable set size of distractors (Hulleman & Olivers, 2017; Kristjánsson & Egeth, 2020; Treisman & Gelade, 1980; Wolfe, 2010; Wolfe & Horowitz, 2004, 2017; Richards et al 2019a; Eckstein 2011)-- the MILO task requires participants to select all items in a sequence (e.g., the numbers 1 through 8) by directly clicking on them in order (Figure 1). The requirement to search and respond in a specific order – a feature that distinguishes MILO from other recent multiple-target tasks (e.g., Cain et al., 2012; Hills et al., 2012, 2013; Kristjánsson et al., 2014; Pellicano et al., 2011; Wolfe et al., 2019) – makes it possible to assess how well participants plan ahead during search, and also whether items that have already been located can be effectively ignored (i.e. inhibited) at later stages of the sequence.

While the MILO task overlaps in many respects with the TMT, the ability to record the time of each response in the sequence, and the ability to manipulate the display in real-time have led to several novel findings. First, it can be shown that participants consistently plan ahead when engaged in sequential search. Such planning is most obvious at the start of the sequence, reflected in a highly elevated first response time compared to all other responses in the sequence (Thornton & Horowitz, 2004;2020a,b; Basoudan et al., 2019). However, using a

“shuffle” manipulation, in which the identities -- not the locations -- of items ahead of the current target are switched in real-time, it has also been shown that such planning occurs up to four items ahead (Thornton & Horowitz, 2004, 2020a; see Kosovicheva et al., 2020 for related findings).

Second, by introducing a manipulation in which items either “Vanish” or “Remain” visible when selected, it can be shown that participants have almost perfect memory for locations that have already been visited. When items vanish from the display, it is clear that search should accelerate at later stages of the sequence, as the set size becomes physically smaller. The novel finding in cognitively healthy adults with the MILO task, is that the Remain condition RT x set size function almost completely overlaps with that of the Vanish condition (Thornton & Horowitz, 2004; 2020a,b). That is, items that have been selected but remain visible are treated by the visual system as if they are no longer visible. It has been suggested that the ability to effectively ignore previously selected targets in this way relies on some form of intact “inhibitory tagging” mechanisms operating on the locations of those items (Thornton & Horowitz, 2004). Such inhibitory tagging in the MILO task has been shown to be location rather than object-based, as the identity between the Vanish and Remain curves breaks down as soon as either local or global motion is added to a display (Horowitz & Thornton, 2008).

Finally, it has recently been shown that such inhibitory tagging is highly sensitive to overall processing load. That is, when task difficulty is increased by requiring participants to alternate between two sequences – as in TMT-B – they are no longer able to ignore past locations, and the Vanish and Remain conditions give rise to RT functions that begin to diverge towards the end of the sequence (Thornton & Horowitz, 2020b). As discussed next, this apparent relationship between processing load and inhibitory mechanisms provides the main motivation for using the MILO task in the current study.

The Current Study

The purpose of the current study was to establish whether the MILO task can be used to identify specific performance deficits in participants with VCI. Our particular focus was on comparing performance in the Vanish and Remain conditions. That is, in addition to a general slowing of response times and an increase in errors rates, we expected search to be compromised for VCI participants when target items remained visible after selection i.e., that in the Remain condition participants with VCI would no longer be able to ignore locations that have already been visited. This prediction follows from the idea that successful inhibitory

tagging and control places demands on general cognitive/attentional resources (Thornton & Horowitz, 2020b) and evidence that VCI is characterized by deficits in such functions (Pantsiou et al 2018, Dichgans & Leys 2017; Vasquez & Zakzanis 2015, Wallin et al 2018). Furthermore, our previous findings of significantly abnormal TMT-B performance in individuals with VCI (Richards et al 2019a,b) -- indicating that higher processing loads cause disproportionately poorer processing in VCI compared to cognitively healthy ageing – suggests that this group will be particularly compromised when MILO targets remain visible, even without the additional requirement of interleaving sequences

We compared the performance of VCI participants with a group of age-matched, cognitively healthy (CH) adults. We additionally included a control group of young adults, to provide an overall baseline for MILO performance, directly comparable to previous MILO studies (Thornton & Horowitz, 2020a,b). Although we did not manipulate the forward planning component of MILO in the current study, we also examined the speed of initial responses, as this component of the MILO response function has previously proven useful in identifying age-related performance factors (Basoudan et al., 2019) and thus may further help to characterise VCI.

Methods

Ethics

The study protocol was approved by the NHS Health and Research Authority Wales Research Ethics Committee 6, and Research and Development, Cardiff and Vale University Health Board. Written informed consent was obtained from all participants.

Participants

Data were obtained from 75 individuals, who were categorised into one of three groups: a VCI patient group (n=26); a cognitively healthy (CH) older adult control group (n=23) and; a young adult (YA) group (n=26). In the following subsections, we provide detailed demographics and recruitment details for each of these groups (see also, Table 1). Sample size was determined primarily by the availability of the relevant patient group. However, *a priori* power analysis conducted as part of a previous MILO study (Thornton & Horowitz, 2020a) indicates that a minimum of nine participants per group is sufficient to detect RT differences of interest in healthy young adults. Our use of a larger sample size was thus conservative, based on the assumption that data from the VCI and CH groups may be more variable. All participants

had normal or corrected to normal vision and hearing, cognitive and physical ability to be able to complete the tasks, fluency in English and mental capacity to provide informed consent. Exclusion criteria included no clinically significant neurological, psychiatric or medical condition, no significant psychoactive drugs and no history of substance or alcohol dependency. The use of prescribed and non-prescribed medication was recorded but not controlled. Payment was not provided for participation. Travelling expenses were however reimbursed.

VCI patient group: Patients with VCI were recruited on an incident patient basis from the Memory Clinic at University Hospital Llandough, Wales, UK. An invitation letter which included a participant information sheet, researcher contact details, an opt-in form and pre-paid envelope, was sent to all who expressed an initial interest in participation. All were diagnosed with minor or major neurocognitive disorder associated with lacunar infarcts and ischaemic white matter lesions as the main type of brain lesions, which included those located subcortically (Skrobot et al 2018; Hachinski et al 2006, see also Richards et al 2019a,b). Diagnosis was made after comprehensive assessment according to normal clinical practice. This included neuroimaging (CT scan, or MRI scan if requested), detailed clinical history, routine laboratory tests, and a neuropsychological test battery assessing executive function, attention, memory, language, visuospatial function (Addenbrooke's Cognitive Examination III; Hsieh et al 2013); the Montreal Cognitive Assessment (MoCA; Nasreddine et al 2005), premorbid ability 'National Adult Reading Test' (NART; Nelson and Willison 1991) and mood, using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983). For inclusion, cognitive impairment had to be of mild to moderate severity (MoCA score between 12 and 25 and/or ACE-III score between 50 and 90).

Exclusion criteria included any likely contributory cause of cognitive impairment other than cerebrovascular disease. The CT and MRI scans were those performed for diagnostic purposes and were examined with respect to the presence of subcortical and cortical infarcts and LA, mass lesions, focal atrophy or other pathology. The extent of white matter change was assessed using the age-related white matter changes rating scale (ARWMC; Wahlund et al., 2001), with 0 = no lesions, 1 = focal lesions, 2 = beginning of confluence lesions, 3 = diffuse involvement of the entire region. Assessment was undertaken by two experienced professionals in the field (AB and AT) who independently rated each scan, yielding a 93% consensus rate, the remaining scores were agreed by further discussion and consensus.

Cognitively healthy older adult controls (CH): The CH group were recruited from relatives of patients attending the Llandough Memory Clinic and participating in this study, and from research volunteers from the Centre for Innovative Ageing (CIA), the Centre for Ageing and Dementia Research (CADR) and the older adult research volunteer database at Swansea University. Inclusion criteria included a MoCA score of > 25 and exclusion criteria included significant self-reported cognitive change or impairment, or past visits to their general practitioner or memory services regarding such concerns. The CH group was age-matched as closely as possible to the VCI group. Neuroimaging was not available for the control group.

Young adults (YA): The young adult group had no self-reported history or evidence suggestive of cognitive impairment. They were recruited from the student members of Swansea University and the local community, CADR and social media. Inclusion criteria included, age 20-27 years and MOCA score >25.

Equipment and procedure

The experiment was conducted using an iPad for both stimulus presentation and response collection. The iPad had a screen dimension of 20 x 15 cm and an effective resolution of 1024 x 768 pixels. The iPad was always placed flat on a desk in landscape mode ensuring there was no reflective light shining on the screen that might obscure or reduce the clarity of the stimuli. While viewing distance was not fixed, we estimated that it was approximately 50 cm from screen surface to the eyes.

The MILO app.

The MILO app was custom written in objective-C using Xcode and Cocos2d libraries. For full details on the functionality of the app and how it can be obtained, see Thornton & Horowitz (2020a). Here, we note that both the app and the source code can be freely obtained by contacting the authors. A cross-platform online version of the task can be previewed by visiting <https://maltacogsci.org/MILO/DEMO/>

Stimuli.

The basic MILO display is shown in Figure 1. In the current study, the MILO task always consisted of the digit sequence 1-8, presented as red and white pool balls with additional shading to provide a slight 3D effect. See Thornton & Horowitz (2020a,b) for details on how this basic sequence can be easily amended for other research purposes. Each ball had a diameter

of 98 pixels or approximately 2° visual angle. At the start of each trial, the eight balls were positioned within an invisible 4 x 4 grid that was centred on the screen. The position of each ball within the grid was randomly chosen on a trial by trial basis, and an additional random offset of up to 80 pixels horizontally and 30 pixels vertically was added to each item to reduce the regularity of the display.

Task.

On each trial, the aim of the MILO task was simply to tap each ball in consecutive order (from 1 to 8), as quickly and accurately as possible. If an error in the sequence occurred, the trial would immediately stop and feedback in the form of a sad emoji face was provided. Incorrect trials were immediately replaced with a new, random trial. At the end of a correct trial or a feedback screen, there was a 2 second blank inter-trial interval, after which the next trial began automatically. In the Vanish condition, items were removed from the screen following the response, with the physical set-size reducing after each selection. In the Remain condition, items were unaffected when touched and the display and set size were the same throughout a given trial. Participants were instructed to begin responses as soon as the display appeared. Although speed was emphasised, there was no time limit and no feedback was provided on trial speed.

Procedure.

Participants completed two blocks of 20 correct trials, one block of Vanish trials followed by one block of Remain trials. If a mistake was during a block, the trial stopped, and was immediately replaced with a new, random display. Data collection thus continued until 20 correct trials were complete. As the Remain condition was known to substantially increase task demands and following prior MILO studies (Thornton & Horowitz, 2020a,b) and the protocol for TMT administration (Bowie & Harvey, 2006), this condition was always completed after the Vanish condition. Prior to data collection, participants were informed about the nature of the task using identical written and verbal instructions. They were asked to respond with the index finger of their dominant hand and to keep their hand at the edge of the iPad. It was stressed that they should start performing the task as soon as the stimuli appeared on screen and to tap each ball as quickly and accurately as possible. For both the Vanish and Remain conditions, the researcher completed one trial as a demonstration, after which the participant performed 3 practice trials. The practice trials also ensured that participants were able to physically and correctly tap the screen and that responses were not hindered by factors such as

long nails (Jenkins et al 2016). The three practice trials were not included in the analysis. Immediately upon completion of the practice phase the program reverted to the testing mode and participants completed the 20 correct trials of the current block.

Data Analysis.

Data files were extracted directly from the iPad. See Thornton & Horowitz (2020a) for additional information about data file format and processing. To assess overall performance, we calculated median completion time and total errors per participant across the 20 trials in each block. These values were averaged across participants using the same 3 (Group: YA, CH, VCI) x 2 (Condition: Vanish/Remain) design. We used a mixed ANOVA to analyse the mean results, with Group as a between subject factor and Condition as a repeated measure.

To more fully capture response patterns within each trial, we calculated the serial reaction time (SRT), the time elapsed since the last event (Thornton & Horowitz, 2004). For the first target, this is the time from display onset. For all other targets, this is the time since the previous item was selected. For each participant, we calculated the median SRT at each target position across the 20 repetitions within a block. As our previous studies have shown qualitative differences between the response to the first target (T1) and all subsequent targets (T2-T8), we analysed these two components separately. T1 responses were analysed using a 3 (Group) x 2 (Condition) ANOVA, and T2-T8 responses with a 3 (Group) x 2 (Condition) x 7 (Target) ANOVA. We used an alpha level of 0.05. We adjusted this level with a Bonferroni correction for all pairwise and post-hoc comparisons. When Sphericity violations were detected on repeated measures, these were corrected by adjusting the relevant degrees of freedom using the Greenhouse-Geisser method.

Data Availability.

The raw data and full summary statistics are available on the OSF page associated with this paper at <https://osf.io/gw2ae/>

Results

Figure 2 (upper panel) shows overall completion time as a function of Group (YA/CH/VCI) and Condition (Vanish/Remain). There was a main effect of Group, with a stepwise increase of approximately two seconds between each category, $F(2,72) = 69.4$, $MSE = 4.0$, $p < 0.001$, $\eta_p^2 = 0.66$. Post-hoc tests confirmed that all pairwise comparisons were significantly different ($ps < .001$). There was also a main effect of Condition, $F(1,72) = 26.2$, $MSE = 3.0$, $p < 0.001$, $\eta_p^2 = 0.27$, with overall slower responses for Remain ($M = 6.4s$, $SE = 0.19$) compared to Vanish ($M = 5.9s$, $SE = 0.15$) trials. However, this effect needs to be interpreted in the context of the significant Group x Condition interaction visible in Figure 2, $F(2,72) = 10.6$, $MSE = 3.0$, $p < 0.001$, $\eta_p^2 = 0.23$. Post-hoc t-tests confirmed that there were significant differences between Vanish and Remain trials for both the CH and VCI groups ($ts > 3$, $ps < .01$), but not for the YA group, $t(25) = 0.5$, n.s.

The average number of error trials as function of Group and Condition are shown in the lower panel of Figure 2. Although, as expected, error rates were very low, there was a main effect of Group, $F(2,72) = 7.7$, $MSE = 4.4$, $p < 0.01$, $\eta_p^2 = 0.18$. Post-hoc comparisons indicated that the VCI group made significantly more errors than either the YA ($p < .05$) or CH ($p < 0.01$) group, while the YA and CH groups did not differ from each other. There was no main effect of Condition, $F(1,72) = .05$, $MSE = 1.6$, $p = 0.82$, $\eta_p^2 = 0.001$ and no Group x Condition interaction, $F(2,72) = 0.85$, $MSE = 1.6$, $p = 0.43$, $\eta_p^2 = 0.02$.

Overall SRT patterns are summarized in Figure 3, as a function of Group and Condition. Each group had the expected elevated first response (T1) followed by a more rapid tail section (T2-T8) which accelerate towards the end of the sequence. While the Vanish and Remain curves largely overlap, there is a slight separation for the CH group at the latter stages of the sequence, a pattern which is amplified for the VCI group. The separation of Vanish and Remain can more clearly be seen by plotting the difference scores for early (T1-T4) and late (T5-T8) responses, as shown in the lower panel of Figure 3.

Analysis of T1 responses (Figure 4) showed only a main effect of Group, $F(2,72) = 43.1$, $MSE = 0.34$, $p < 0.001$, $\eta_p^2 = 0.55$. The relative pattern of slowing mimics that seen for overall completion time (Figure 2), and post-hoc tests again confirmed that all pairwise comparisons were significantly different ($p < .001$). However, there was no effect of Condition, $F(1,72) = 0.92$, $MSE = 0.05$, $p = 0.34$, $\eta_p^2 = 0.01$, and no Group x Condition interaction, $F(2,72) = 0.97$,

MSE = 0.05, $p = 0.39$, $\eta_p^2 = 0.03$. For the sake of completeness, the second panel in Figure 4 plots the overall completion times with the T1 responses removed, further illustrating that Vanish/Remain differences appear to occur in later stages of the sequence.

In the initial Group x Condition x Target analysis of the T2-T8 responses, all main effects and interactions were significant. Of particular note, there was a main effect of Group, $F(2, 72) = 58.0$, MSE = 0.4, $p < 0.001$, $\eta_p^2 = 0.62$, with all pairwise comparisons significantly different, and a three-way Group x Condition x Target interaction, $F(9.2, 329.5) = 2.3$, MSE = 0.01, $p < 0.05$, $\eta_p^2 = 0.06$. The full results are summarized in Table 2. Here we focus on reporting the planned follow-up analyses for each group separately, which is the most concise way to explore the differential SRT patterns.

For the YA group, the SRT pattern exactly replicated what we have seen in previous studies using participants of comparable age (e.g., Thornton & Horowitz, 2004;2020a,b). Specifically, the Vanish and Remain patterns very closely overlap, particularly towards the end of the sequence where both conditions give rise to an accelerating function. There was a main effect of Target, $F(3.6, 89.6) = 27.2$, MSE = 0.02, $p < 0.001$, $\eta_p^2 = 0.52$, but no main effect of Condition, $F(1, 25) = 0.2$, MSE = 0.005, $p = 0.63$, $\eta_p^2 = 0.01$, and no Condition x Target interaction, $F(3.1, 77.5) = 2.3$, MSE = 0.01, $p = 0.08$, $\eta_p^2 = 0.08$.

For the CH group, in addition to a main effect of Target, $F(6, 132) = 58.2$, MSE = 0.01, $p < 0.001$, $\eta_p^2 = 0.73$, there was also a significant main effect of Condition, $F(1, 22) = 14.8$, MSE = 0.01, $p < 0.01$, $\eta_p^2 = 0.4$. On average, Remain responses ($M = 0.65$ s, SE = 0.02) for this group were approximately 60 ms slower than Vanish responses ($M = 0.59$ s, SE = 0.02). However, despite an apparent separation of the two SRT functions towards the end of the sequence, visible in Figure 3, the Condition x Target did not approach significance, $F(6, 132) = 1.3$, MSE = 0.01, $p = 0.26$, $\eta_p^2 = 0.06$.

This contrasts with the VCI group, where the pattern of responses is dominated by the Conditions x Target interaction, $F(4.4, 109.5) = 5.6$, MSE = 0.02, $p < .001$, $\eta_p^2 = 0.18$, as the Vanish SRT curve accelerates more quickly than the Remain curve towards the end of the sequence. This effect is the dominant feature of the lower panel of Figure 3. Both the main effect of Target, $F(3.7, 92.9) = 45.6$, MSE = 0.04, $p < 0.001$, $\eta_p^2 = 0.64$, and the main effect of Condition, $F(1, 25) = 20.2$, MSE = 0.07, $p < 0.001$, $\eta_p^2 = 0.45$, were also significant. For the VCI group, Remain responses ($M = 0.97$ s, SE = 0.06) were on average 130 ms slower than Vanish responses ($M = 0.84$ s, SE = 0.05).

Discussion

In the current study, we used the MILO task to assess the performance of a group of older adults diagnosed with mild to moderate VCI. Our goal was to shed additional light on the behavioural consequences of the white matter changes typically associated with VCI. Compared to cognitively healthy, age-matched control participants, the performance of VCI participants was characterised by overall slowing, increased error rates, and crucially, a compromised ability to ignore previously visited locations. This latter effect was identified using the Vanish/Remain manipulation, where the SRT functions diverged towards the end of the sequence, with slower responses when the physical set size did not reduce after each selection. In the remainder of this discussion, we examine the behavioural patterns of each group in more detail, before drawing some general conclusions.

The MILO pattern observed with the YA group exactly replicates our findings from previous studies (e.g., Thornton & Horowitz, 2004;2020a,b). The elevated first response is followed by an accelerating tail, in which Vanish and Remain conditions give rise to overlapping functions. This replication adds to the growing evidence that forward planning and inhibitory control are two key components of search behaviour and demonstrates that the MILO task is a reliable tool for exploring them.

Focusing on the overlap between Vanish and Remains conditions, in our original MILO study (Thornton & Horowitz, 2004), we suggested that this ability to ignore the location of previously visited targets likely relies on some form of automatic inhibitory tagging. We further proposed that the most likely candidate mechanism for such tagging would be inhibition of return (IOR; Posner & Cohen, 1984; Satel et al 2019), in its role as a foraging facilitator (Klein, 1988; Klein & MacInnes, 1999; Tipper et al., 1994; see Wang and Klein 2010 for review). In this role, IOR is thought to act as an automatic inhibitory system that “marks multiple previously attended locations” (Satel et al., 2019, p3), biasing search away from distractors (Campana & Casco, 2009) towards novel items.

In the MILO task, however, the status of “distractor” only evolves over time, with previously visited items also having been the target of an explicit motor response. As discussed in Thornton & Horowitz (2004), the ability to ignore past target items could thus also involve other forms of implicit/explicit memory for location or some form of response-level tagging in addition to mechanisms such as IOR. Indeed, our recent finding that the ability to ignore past locations is disrupted with increases in intrinsic attentional load (Thornton & Horowitz,

2020b), perhaps hints at a more explicit or active mechanism of tagging, although we note that IOR can also be disrupted under some forms of dual-task load (e.g., Castel et al., 2003; Vivas et al., 2010; Zhang & Zhang, 2011). For now, while the ability to ignore past locations MILO appears to be well-established, the precise nature of the mechanism(s) involved must await further investigation, and the term “inhibitory tagging” should be interpreted in a very general sense.

The MILO patterns for the CH group differed in two key respects from the YA group. First, their responses times were generally slower overall. Second, and more interestingly, their Remain responses were consistently slower than their Vanish responses. This latter finding indicates that the behaviour of CH participants was influenced by the additional visual clutter, or distracters, when targets remained visible. We have seen this form of constant offset in previous studies with young adults, but typically when there are additional mediating factors, such as object motion (Horowitz & Thornton, 2008), or interleaved Vanish and Remain trials (Thornton & Horowitz, 2020a), rather than static, blocked conditions as in the current study. Here, the additional processing load associated with “tagging” old targets (Watson & Humphreys, 1997) or some form of visual or motor interference or distraction, from the old targets, affects CH participants across the entire sequence. It is important to note that although there appears to be a visible trend for the slowing in Remain trials to increase at later stages of the sequence (Figure 3), there was no hint of a Condition x Target interaction, suggesting that overall CH participants were able to ignore past target locations.

In contrast, the behavioural pattern of the VCI group is dominated by a clear separation between the Vanish and Remain conditions at later stages of the SRT function (Figure 3). This separation, while visible in the raw SRT patterns, is emphasised in the difference score panel of Figure 3. Compared to age-matched, cognitively healthy controls, then, the VCI participants were overall slower, but also had a more emphatic difference between Vanish and Remain conditions towards the end of the sequence. This indicates that the response to the Remain stimuli no longer resembled those evoked in response to stimuli that have actually vanished.

How do we explain this pattern? Following from our analysis of the YA pattern above, the most parsimonious explanation would seem to be to suggest that VCI is associated with a reduction in the ability to successfully use inhibitory tagging, broadly defined. Such a deficit would mean that past targets continue to have a detrimental, i.e., slowing, effect upon subsequent responses. As already noted, we do not know the precise nature of the mechanism that typically achieves suppression of Remain locations during MILO. We note, however, that IOR is mediated in part by the same cortical and subcortical (e.g., superior colliculus) structures

(Bastos Leite et al 2006; Sung et al 2009, Sapir et al 2004) commonly affected in VCI (Sung et al 2009, Kalaria et al 2016). While this observation is suggestive that an IOR deficit could contribute to the Remain pattern of the VCI group, we clearly can't rule out deficits in other forms of inhibitory and/or memory-based tagging mechanisms. An interesting future direction would be to directly probe for specific issues with IOR while at the same time measuring MILO performance in a group of VCI participants.

Could the divergence in Vanish and Remain functions in VCI be explained in terms of “goal neglect” or simply forgetting the next target in the sequence, rather than a failure to ignore past locations? While possible, we feel this explanation is unlikely for a number of reasons. First, to overcome a similar “confusion” issue during Vanish trials, we would need to assume that participants switch to a different strategy to find the next target when items are disappearing, otherwise the two SRT functions would still overlap. That is, during Vanish trials, rather than prospectively searching for the next target in the sequence, as instructed, participants might instead rely on identifying the highest number still visible on the screen. While we have not tested this idea – which could be done by adapting MILO to use monotonic sequences with randomly varying increments which cannot be predicted from trial-to-trial – our suspicion is that the basic SRT functions would look quite different to when there is a simple plus-one numeric progression. We also note, that using a “find the highest value” strategy during Remain trials without the ability to ignore past locations would predict a completely flat SRT function, which is clearly not the case.

Second, behaviourally, VCI is characterised by deficits in executive function with memory functions relatively preserved (Gorelick et al., 2011). Individuals with a “mild to moderate” VCI classification, as here, are very unlikely to have problems remembering or indexing through a highly overlearned sequences such as the digits 1-8. Indeed, issues with executive function would probably suggest they are more likely to avoid the need to have to switch strategies between blocks of trials.

Third, problems with remembering the next target in the sequence should also predict much higher absolute error rates, and, crucially, differential error rates between Vanish and Remain conditions, neither of which is observed in the current data set. While error rates were higher in the VCI group compared to both the CH and YA groups, examination of Figure 2 shows that at most, participants were making on average between two and three error responses per block of 20 trials, which required a total of 160 correct responses. If they were confused about the next target in the sequence, this would almost certainly have led to more error responses. More importantly, if they were only confused during Remain blocks and/or using a different strategy

in Vanish blocks, then error rates for the VCI participants in these two conditions might be expected to substantially diverge, which it does not.

To summarise, then, our preferred explanation for the pattern of VCI data, is to suggest that the slowing of Remain SRTs occurs due to a breakdown in the ability to effectively ignore past target locations and that this breakdown amounts to a lack of inhibitory control. Determining whether such problems with inhibitory control in VCI reflects a deficit in a particular mechanism, for example IOR, or occurs as a consequence of more general inability to cope with increased cognitive load (Thornton & Horowitz, 2020b) will require further investigation.

Conclusions

In the current paper, we have demonstrated that the MILO task can be a useful tool for identifying non-age-related changes in behaviour in patient populations. While increased overall completion times were observed in both VCI and age-matched controls, the simple MILO Vanish/Remain manipulation was able to provide a clear behavioural signature that distinguished between them. As pathological change in white matter can be silent and not visible in routine neuroimaging (Richards et al 2019a), developing tests that are able to identify subtle changes in brain function and behaviour is crucial. Furthermore, if our interpretation of this pattern as an indication of inhibitory control issues in VCI is confirmed, such a finding could have a number of important implications. Not only might this help explain, at least in part, why individuals with VCI are over-distractable and show a decline in selective attention (Richards et al 2019a), but it could also predict performance deficits for many everyday tasks that require sequences of action. For example, the inability to ignore irrelevant but distracting information is likely to detrimentally influence behaviours such as driving which are highly dependent upon visual search for their efficient and safe execution (McManus et al 2017). To conclude, we suggest that the measurement of RT in action-related scenarios together with assessment of general inhibitory control in clinical practice may help to inform the real-life impact of the disease per se, and how such functional change relates to disease progression.

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Table 1.

Participant Demographics. Group Mean results. Standard deviation in parenthesis

	YA n = 26	CH n =23	VCI n =26
Mean Age in years	20.9 (1.81)	74.7 (5.58)	76.5 (4.64)
Age range	20-27	69-86	68-83
Gender	34.6% Males 65.4% Females	21% Males 78.3% Females	57.7% Males 42.3% Females
Mean years in education	16.46 (1.53)	16.22 (4.11)	13.04 (2.63)
Educational range	12-20	10-24	10-21
Mean (sd) MoCA Score	28.5 (1.1)	28.39 (1.37)	20.46 (3.01)
Mean (sd) HADS score: Anxiety	7.34 (3.3)	5.22 (3.74)	6.04 (3.36)
Mean HADS (sd) score: Depression	3.5 (3.73)	2.22 (2.45)	4.35 (3.21)
White matter load Mean (sd) ARWMC score	-	-	1.23 (1.03)

Table 2

Results for the 3 (Group) x 2 (Condition) x 7 (SRT) mixed ANOVA conducted on the T2-T8 SRT patterns

Factor	df	MSE	F	η_p^2
Group	2,72	0.4	58.0***	0.6
Cond	1,72	0.1	30.6***	0.3
Cond * Group	2,72	0.1	11.5***	0.2
SRT	4.6,327.7	0.1	119.7***	0.6
SRT * Group	9.1,327.7	0.1	4.9***	0.1
Cond * SRT	4.6, 329.5	0.1	6.7***	0.1
Cond * SRT * Group	9.2, 329.5	0.1	2.3*	0.1

*** $p < .001$; * $p < .05$

FIGURE 1. MILO Display

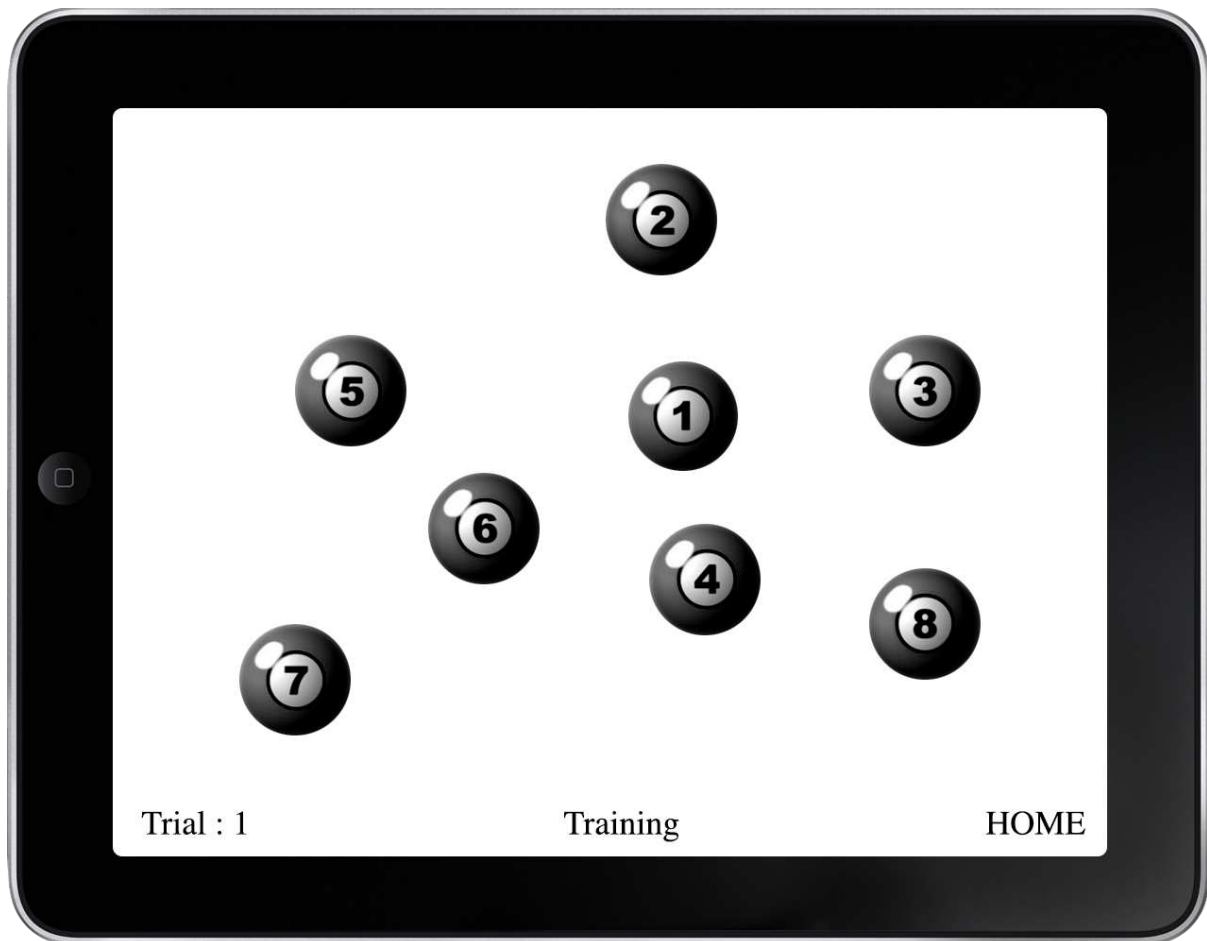


FIGURE 2 – Overall Completion Time (s) and average number of errors as a function of experimental group (YA = Young Adult; CH = Cognitively Healthy Older Adults; VCI = Vascular Cognitive Impairment) and MILO condition. Error bars indicate 1 standard error of the mean.

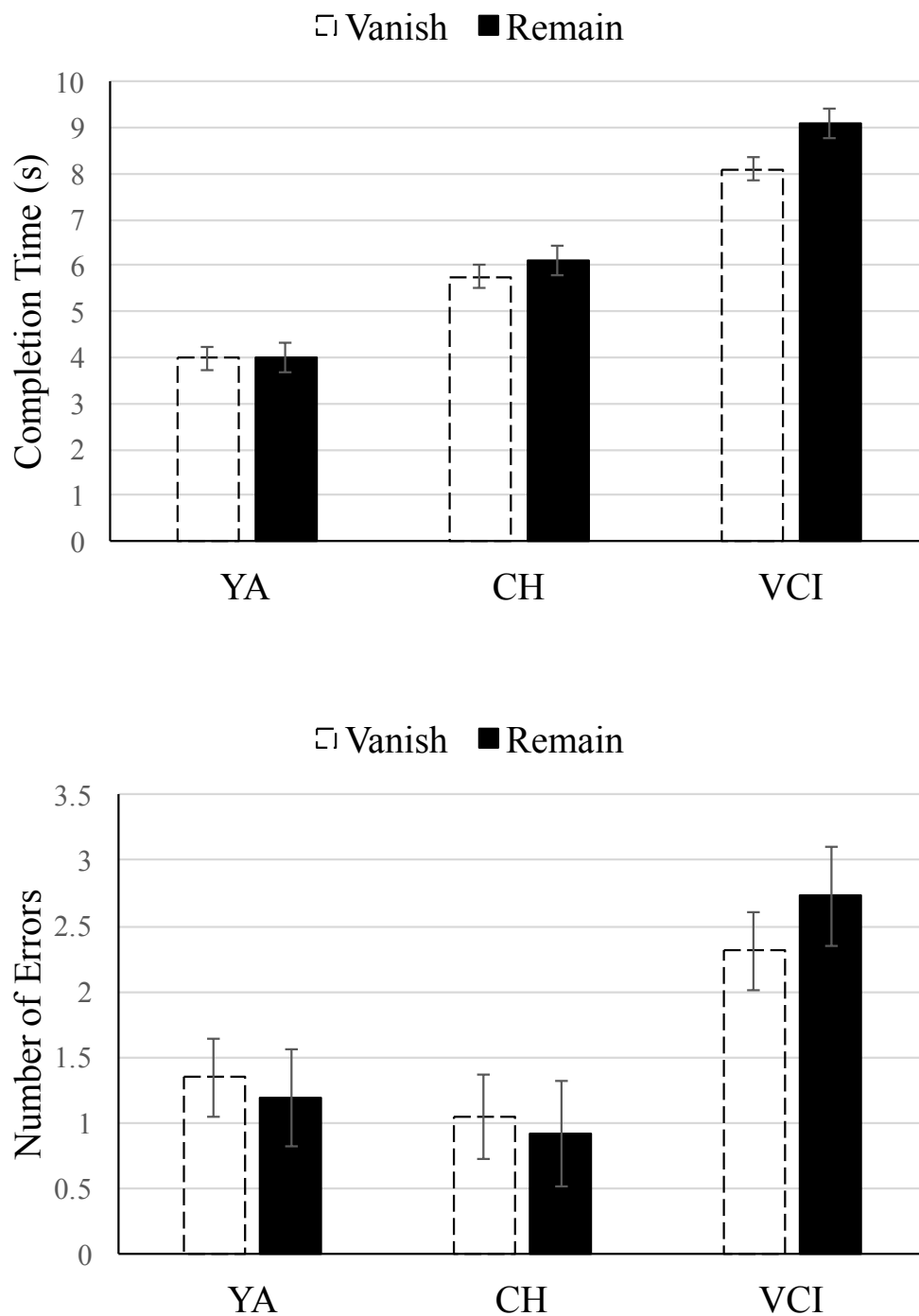


FIGURE 3 – Upper panel: Overall SRT patterns for each experimental group (YA = Young Adult; CH = Cognitively Healthy Older Adults; VCI = Vascular Cognitive Impairment) as a function of target item and condition. Lower panel: Average Remain-Vanish differences collapsed across early (T1-T4) and late (T5-T8) items of the SRT function. Error bars indicate 1 standard error of the mean.

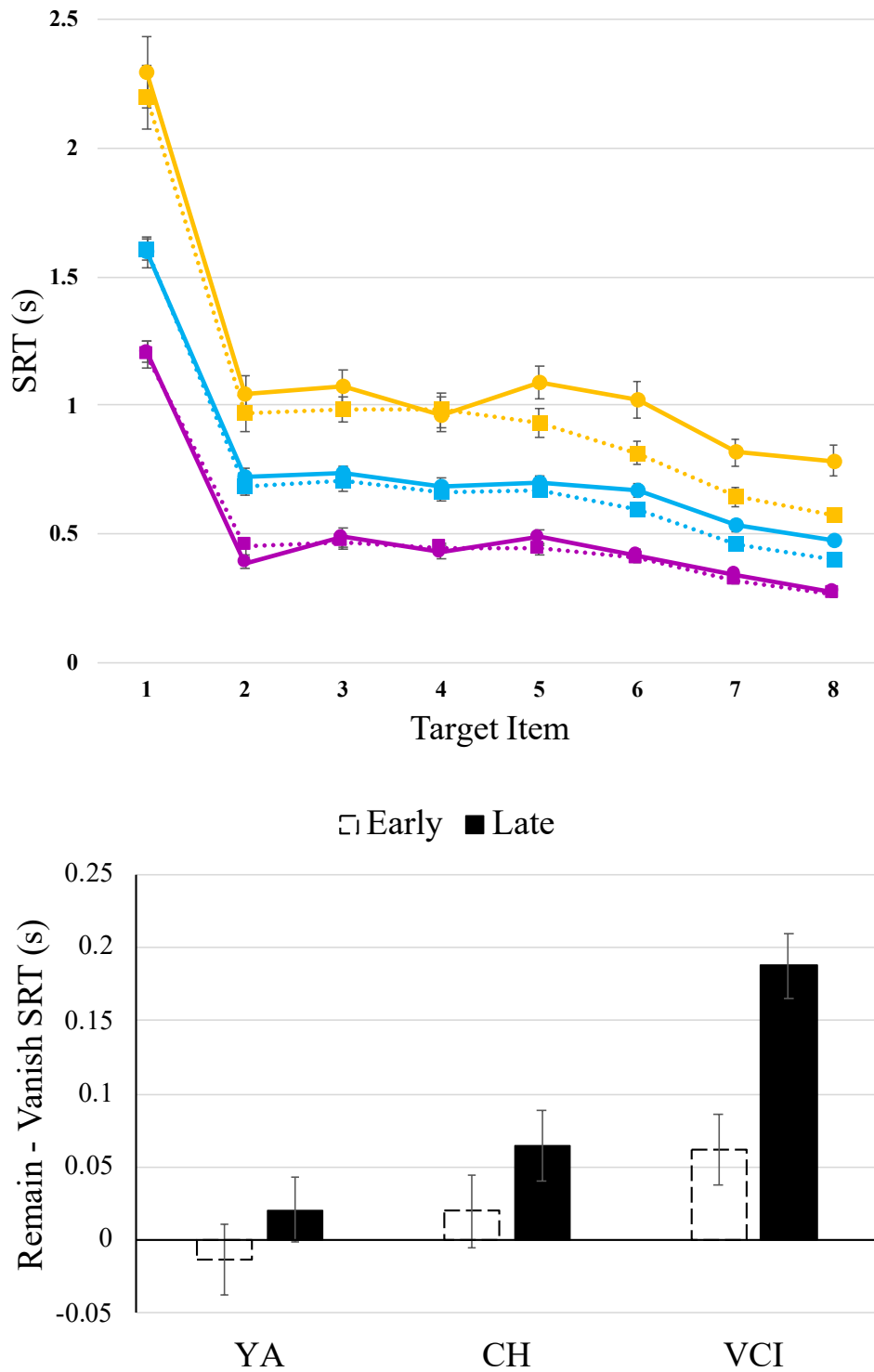


FIGURE 4 – T1 Responses and RT8-RT1 (overall completion times with the T1 responses removed) averages as a function of experimental group (YA = Young Adult; CH = Cognitively Healthy Older Adults; VCI = Vascular Cognitive Impairment) and MILO condition. Error bars indicate 1 standard error of the mean.

