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Abstract

In complex visuomotor tasks, such as cooking, people make many saccades to continuously search for items before and during reaching movements. These tasks require cognitive resources, such as short-term memory and task-switching. Cognitive load may impact limb motor performance by increasing demands on mental processes, but mechanisms remain unclear. The Trail-Making Tests, in which participants sequentially search for and make reaching movements to twenty-five targets, consist of a simple numeric variant (Trails-A) and a cognitively challenging variant that requires alphanumeric switching (Trails-B). We have previously shown that stroke survivors and age-matched controls make many more saccades in Trails-B, and those increases in saccades are associated with decreases in speed and smoothness of reaching movements. However, it remains unclear how patients with neurological injuries, e.g., stroke, manage progressive increases in cognitive load during visuomotor tasks, such as the Trail-Making Tests. Importantly, switching between numbers and letters leads to progressive increases in cognitive load as Trails-B progresses. Here, we show that stroke survivors with damage to frontoparietal areas and age-matched controls made more saccades and had longer fixations as they progressed through the twenty-five alphanumeric targets in Trails-B. Furthermore, when stroke survivors made saccades during reaching movements in Trails-B, their movement speed slowed down significantly. Thus, damage to frontoparietal areas serving cognitive motor functions may cause interference between oculomotor, visual, and limb motor functions, which could lead to significant disruptions in activities of daily living. These findings augment our understanding of the mechanisms that underpin cognitive motor interference during complex visuomotor tasks.

NEW & Noteworthy

We used a neuropsychological test called the Trails-Making-test and analyze patterns of eye and reaching movements in controls and stroke survivors. We characterized how gaze and reaching movements change within a trial in the easier Trails-A and the more cognitively challenging Trails-B variant that requires alphanumeric switching. We found that as the Trails-B trial progressed stroke survivors made more saccadic eye movements and longer fixations that likely contributed to slowing down of reaching movements.

Introduction

During activities of daily living, humans continuously perform eye movements that shift their gaze to search for task-relevant information and then initiate limb and body movements to achieve task goals. For example, humans continuously shift their gaze while driving to search for traffic lights, street signs, and vehicles before making limb movements to manipulate the pedals and steering wheel (Land and Horwood 1995; Summala et al. 1996; Hayhoe and Ballard 2005). While making a meal, humans continuously shift their gaze to search for ingredients and cookware before initiating and while performing movements used to grasp, transport, and manipulate key items (Ballard et al. 1995). While it is easily taken for granted that we actively move our eyes several times a second to search for task-relevant information (Carpenter 1988), visual search is a highly evolved function that is regulated by *top-down* executive processes that interact with bottom-up sensory processes. Top-down executive processes use knowledge from previous experience to shift gaze to locations in which there is a higher likelihood of finding task-relevant information (e.g., spices would likely be stored together in the same cabinet). *Bottom-up* sensory processes preferentially attract attention and shift gaze to salient objects in the visual workspace (e.g., red spice bottle on a white counter) (Wolfe et al. 2003; Horowitz et al. 2006). However, the mechanisms that govern the interplay between visual search and limb motor control are not clear.

Numerous studies have examined reaching movements to a single salient target to advance our understanding of the behavioral features of eye-hand coordination (EHC) and their underlying neural mechanisms (Buneo and Andersen 2006; Vesia and Crawford 2012; Battaglia-Mayer and Caminiti 2019). Most research on this paradigm has focused on *bottom-up* processing of sensory information, with a dominant focus on how visual information is gathered from a single stimulus and used for motor planning (Carpenter 2002; Prablanc et al. 2003; Elliott et al. 2017). The implicit assumption within this paradigm is that the visual system isolates a single stimulus of interest and performs relevant visuospatial computations necessary to enable the motor system to activate muscles to bring the hand to the stimulus. However, real-world situations seldom bestow extraordinary saliency to a single stimulus such that it attracts the attention of an actor exclusively towards itself. In contrast, humans must optimally organize their visual search to quickly retrieve task-relevant information from multiple visual stimuli with competing saliency to efficiently achieve task goals in real-world situations. For example, compared to less experienced counterparts, experienced drivers (Mourant and Rockwell 1972) and surgeons (Hermens et al. 2013) optimize their visual search to efficiently gather task-relevant information. During less demanding activities such as meal preparation, humans make saccades (rapid eye movements) to continuously search for objects of interest before initiating arm and hand movements used to manipulate task-relevant objects (Hayhoe and Ballard 2005). These studies offer a glimpse into the flexible and dynamic interactions between top-down and bottom-up processes used to organize and execute eye and limb movements systems during activities of daily living.

A critical constraint that governs this interaction between the ocular and limb motor systems is that the limbs have much greater inertia than the eyes. As a result, eye movements are faster and require less energy than limb movements. This allows humans to make hundreds of saccades per minute, while only performing limb movements when the identities and locations of task-relevant objects have been established with a degree of certainty. Importantly, the neural mechanisms that govern top-down and bottom-up interactions used to organize and perform eye and limb movements are likely disrupted in patients with neurological disorders, resulting in suboptimal visual search and deteriorated task performance (Corbetta and Shulman 2011).

We have previously provided evidence supporting this hypothesis using the Trail-Making Tests (Reitan 1958), a neuropsychological test used to assess deficits in visual scanning, processing speed, and task-switching. The Trail-Making Test includes two variants, Trails-A in which participants move their hand to draw lines connecting the first 25 positive integers (1, 2, 3, . . ., 25, Fig. 1A), and Trails-B in which participants draw lines alternating between the first 13 positive integers and the first 12 Roman letters (1, A, 2, B, 3, C, . . ., 13; Fig. 1B). Trails-A requires participants to search for the next target in the numeric sequence and then make a reaching movement to the target once it has been identified. Trails-B is more cognitively challenging because it also requires top-down executive control in the form of working-memory and task-switching to identify the next target in the alphanumeric sequence (Reitan 1958).

We found that stroke survivors with mild motor impairments executed significantly more saccades than age-matched controls due to deficits in top-down processes, such as visuospatial planning and working memory that guide visual search (Singh et al. 2017). We then showed that these excessive saccades may interfere with limb movements, leading to worse performance on the Trail-Making Tests (Singh et al. 2018). Specifically, we found that the number of saccades that stroke survivors made during ongoing reaching movements was strongly associated with decreases in the speed and smoothness of reaching movement in stroke survivors. Furthermore, higher numbers of saccades were correlated with difficulties performing daily tasks involving hand function and mobility (measured using Stroke Impact Scale). This suggests that abnormal interactions between top-down executive processes and the limb motor system disrupt functional performance in stroke survivors.

Here, we investigated if visual search and limb motor control are disrupted by increases in cognitive load that occur as participants progressively perform alphanumeric switches during Trails-B. We hypothesized that increases in cognitive load (top-down executive processes) would lead to progressive disinhibition of bottom-up processes, leading to disruption of the visual, oculomotor, and limb motor systems. Support for this hypothesis comes from studies that show that the visual system is more sensitive to bottom-up stimulation when loads on working memory are high (Lavie 2005; Soto et al. 2008). In our task, this would imply that gaze would be reflexively directed to more targets in the workspace as the Trails-B trial progresses. Thus, our first prediction was that progressive increases in cognitive load would cause more saccades to be initiated due to disinhibition of the oculomotor system. Second, we predicted that increases in cognitive load would cause longer fixations due to disruption of visual processing. We have previously shown that the average fixation time over the entire trial was neither different between Trails-A and B nor between the two groups (Fig. 5C in Singh et al. 2017). Despite this similarity between the two Trails tasks, we expected that as participants progressed along the alphanumeric sequence in Trails-B (1,A,2,B,3,C….), recall of every subsequent number or letter would become more cognitively challenging and increase the fixation duration as the trial progressed. This prediction is supported by imaging studies that have shown stronger activation of the dorsolateral prefrontal cortex and other areas of the brain involved in working memory during Trails-B compared to Trails-A (Moll et al. 2002; Zakzanis et al. 2005).

Finally, we predicted that increases in cognitive load would cause slower limb movements and greater eye-hand dyscoordination (EHdC) due to abnormal interactions between the ocular and limb motor systems in both controls and stroke survivors. Previous studies using dual-task paradigms that placed additional attentional demands during reaching movements have shown reduced movement smoothness and increased motor errors and movement time in stroke survivors (Shin et al. 2017; Mullick et al. 2021). Participants in these studies used their affected arm. We expected that increase in cognitive load would also produce greater EHdC in the less-affected arm of stroke survivors. We asked the participants in our study to perform the test with their preferred arm. An overwhelming

majority (11/16) of the stroke survivors preferred to perform the test with their less affected arm. Finally, we predicted that the effects would be greater in stroke survivors, i.e., stroke survivors would make progressively more saccades, longer fixations, and slower limb movements compared to healthy controls. Our predictions for saccades and fixations were supported, but not for reaching movements. While eye hand dyscoordination (EHdC) was stronger in stroke survivors in Trails-B, EHdC did not progressively increase for either group as subjects progressed through the trail.

Methods

The experimental setup and the demographics of the participants have been described in detail in our previous publications (Singh et al. 2017; Singh et al. 2018). Briefly, we recruited 16 stroke survivors (mean age 62, range [48,80], 4 females) and 16 control participants (mean age 60, range [52,70], 10 females). Stroke survivors were included if they had suffered a unilateral stroke at least 6 months before testing in either the middle frontal gyrus or the superior parietal gyrus and had difficulty performing one or more relevant activities of daily living (Stroke Impact Scale-16, one or more individual scores < 5). Participants were excluded if they had a history of a central or peripheral neurological disorder (other than stroke) or a musculoskeletal problem of the tested upper extremity. Stroke survivors were also excluded if they exhibited moderate to severe spasticity of the tested upper extremity (Modified Ashworth Scale score ≥2). All participants were screened for visual impairment and visuospatial neglect, and they had no difficulty understanding and following simple instructions. The Institutional Review Board of the University of South Carolina approved the study. All participants provided informed consent before participating in the study.

Experiments were performed on a KINARM Endpoint Lab (KINARM, Canada) integrated with an Eyelink 1000 remote eye tracker (SR Research, Canada) and an augmented reality display. Limb kinematics were sampled at 1000 Hz and low-pass filtered at 20 Hz. Gaze data were sampled at 500 Hz, preprocessed to remove blinks and corneal reflection artefacts, and low-pass filtered at 20 Hz (Singh et al. 2016). Saccades and fixations were subsequently identified from the gaze data.

Participants performed the Trails-Making test along with a battery of other tests. In this report, we are only reporting the data collected on the Trails-Making test. Also, similar to the paper and pencil version of the Trails-Making test, the traversed reaching trajectory stayed on the display. This could help participants direct their search to only those sections of the workspace where there were unreached targets. We also assessed cognitive impairments using an in-house cognitive screening tool, Visual Cognition Assessment (ViCA). This is a visuospatial analog of the Montreal Cognitive Assessment (MoCA) that uses nonverbal responses for all nonlanguage components of the MoCA (visuospatial/executive, memory, attention, and orientation). The maximum ViCA score could be 20. Control participants (18,[16-20]) scored slightly better on ViCA than stroke survivors (15,[12-20]).

Participants were instructed to complete the tests as quickly as possible. Stroke survivors were instructed to complete the test with their preferred hand post-stroke and controls with their dominant hand. Most stroke survivors preferred to use their less affected, left hand (post-stroke Edinburgh Handedness Inventory, n = 11). There were no differences in performance between stroke survivors who preferred their left or right hand. Participants performed only a single trial of Trails-A and -B within a battery of other eye-hand coordination tasks (not reported here). Before completing the test, participants completed sequences of five practice targets for Trails-A and B.

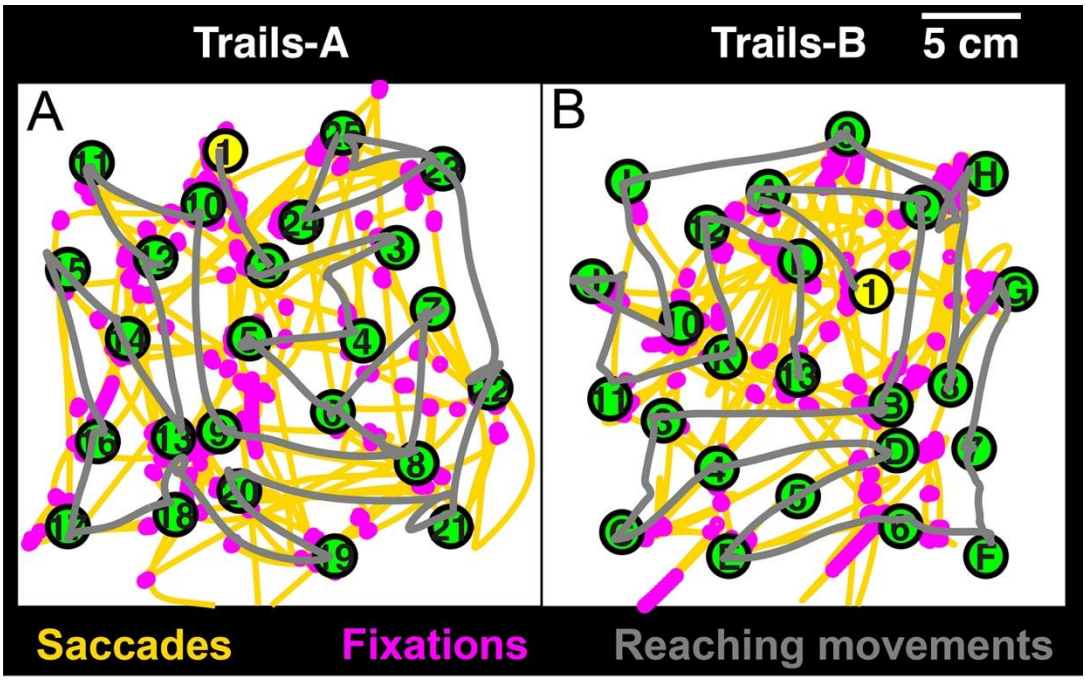

Figure 1: Gaze and hand kinematics during the Trails-Making-Test A (left panel) and B (right panel) for a representative control participant. Saccades are shown in yellow, fixation in pink and the hand reaching movements in grey. Participants cannot see the fixations and saccades, but the reaching trajectories (grey lines) stay on the workspace. Thus, at the very end of the task when only a few targets are left, the grey lines can be used to restrict the visual search in a small area where the remaining targets are.

We examined changes in gaze and reaching behavior as a function of task progression in Trails-A and Trials-B by computing the Number of Saccades, Mean Fixation Duration, and Mean Reach Speed for each sequential pair of targets in Trails-A and Trails-B separately. In contrast to our previous reports (Singh et al. 2017; Singh et al. 2018), here we only counted those saccades that were made to targets that had already been reached. By definition, these saccades are wasteful and should be avoided by participants. In both the paper and pencil version as well as the KINARM version of the Trails test, the traversed limb trajectory stays on the paper (or visual display) and could be used to guide visual search only to the remaining targets. Measures were quantified from the time the hand touched the first target to the time it touched the second target in each sequential pair. Notably, measures were only quantified for each sequential pair between the 1st (P1) and 21st targets (P2). The 21st target was chosen instead of the 25th target due to the spatial layout of the task. The key was to pick one of the targets before the visual search space shrank. Specifically, the search space gradually shrinks between the 1st and 21st targets, but rapidly shrinks between the 22nd and 25th targets. In these small search spaces, both the stroke survivors and controls suddenly produced very few saccades between each sequential pair of targets. Since the choice of the 21st target was

arbitrary, we repeated our analyses with the 22nd target and found qualitatively similar results. Participants, particularly stroke survivors, made some reaching errors (reached to an incorrect target in the sequence). Those erroneous movements were not included in the analysis.

Descriptive statistics are presented in the text and figures as mean ± SE. We performed regressions between the measures and targets for stroke survivors and controls in Trails-A and Trails-B separately. A slope was considered statistically indistinguishable from '0' if its 95% confidence interval spanned both negative and positive numbers. Finally, we used repeated-measures ANOVA with *group* as between-subjects factor (controls and stroke survivors as levels) and *pairs* as the within-subjects factor (first target pair, 1-2, and second target pair, 21-22, as levels) for Trails-A and Trails-B separately. The level of significance was chosen as α=0.05. Effect sizes were calculated using generalized η^2. Normality of the data were tested using the Wilk-Shapiro test. Bonferroni corrections were used for multiple comparisons. To minimize the effects of outliers in our small sample size, we also performed bootstrap tests between the 1st and the 21st targets for both groups. We simulated the null hypothesis that both datasets are sampled from the same distribution. Briefly, we first pool both datasets into a single group and then simulate sampling (with replacement) from the two pools to create two groups. We then compute a test-statistic to compare the two groups and repeated this process 2,000 times and counted how many times we obtained a difference between means as large as the one in the real data. If that turned out to be likely improbable ($p<0.05$), we rejected the null hypothesis. Bootstrap tests perform better with a higher number of iterations. We tried 1000, 2000, and 5000 iterations and found that the results did not change much between 2000 and 5000 and therefore chose 2000 iterations. All data pre-processing and analysis were performed in MATLAB (Mathworks, Natick, MA). All statistical tests were performed in R.

Results

For both Trails-A and Trails-B, the number of saccades made on targets that had already been reached increased for stroke survivors as the trial progressed (Fig. 2A). On average, in Trails-A, controls made 0.44±0.13 and 0.06±0.06 saccades to already reached targets between the first and last target pairs, respectively. Stroke survivors made 0.63±0.20 and 3.44±1.27 for the first and the last pairs, respectively. The slope of the regression line was statistically indistinguishable from 0 for controls, and was positive (0.07, 95% interval [0.02, 0.13]) for stroke survivors. The intercepts were positive and similar for both groups. The statistical model showed a significant main effect of *group* ($p<0.001$, η^2=0.21) and an interaction effect between *group* and *pairs* (p=0.001, η^2=0.16). Post-hoc comparisons revealed significant differences between the two groups at the second target pair (p=0.002) (Fig. 2B). This difference was also confirmed by our bootstrap test (p=0.001).

In Trails-B, controls made 1.0±0.33 and 1.6±0.45 saccades to already reached targets between the first and last target pairs, respectively. Stroke survivors made a slightly higher number of saccades for the first pair, 1.69±0.41, but many more saccades for the final pair, 10.3±3.83. The intercept was larger for the stroke survivors, and the slope was marginally steeper. The intercept for controls was indistinguishable from 0 and for the stroke survivors was 2.7 (95% interval [0.06, 5.4]). The slope for the controls was 0.14 (95% interval [0.07,0.21]) and for the stroke survivors was 0.24 (95% interval [0.04,0.45]) (Fig. 2A). The main effects of *group* (p=0.007, η^2=0.14) and *pairs* (p=0.005, η^2=0.11) were significant. Post-hoc tests showed that the difference between the number of saccades made to previously reached targets at the 21st target between stroke survivors and controls approached significance (p=0.05) (Fig. 2C). The bootstrap test showed that this difference was in fact significant (p=0.025). Thus, we have reported this difference as significant in Fig. 2C. Together, these results suggest that stroke survivors made more saccades than controls in both Trails-A and Trails-B.

Stroke survivors also progressively made more saccades as the trials progressed to previously reached targets at the final target pair.

The results for Mean Fixation Duration (Fig. 3) were similar to the saccades. For controls, the mean fixation duration for the first pair in Trails-A was 0.63±0.25 s and for the last pair was 0.24±0.29 s. For stroke survivors, the fixation duration for the first and final pairs were 0.31±0.11 s and 2.19±0.41 s, respectively. The intercept for the regression was slightly lower for the controls (1.03, 95% interval [0.83,1.25]) than the stroke survivors (1.53, 95% interval [1.0,2.07]). Both the slopes were statistically indistinguishable from 0 (Fig. 3A). The statistical model showed a main effect of *pairs* ($p<0.001$, $\eta^2=0.28$) and an interaction effect between *group* and *pairs* ($p=0.014$, $\eta^2=0.09$). The post-hoc tests showed a significant increase in fixation duration for stroke survivors between the two target pairs ($p<0.001$) (Fig. 3B).

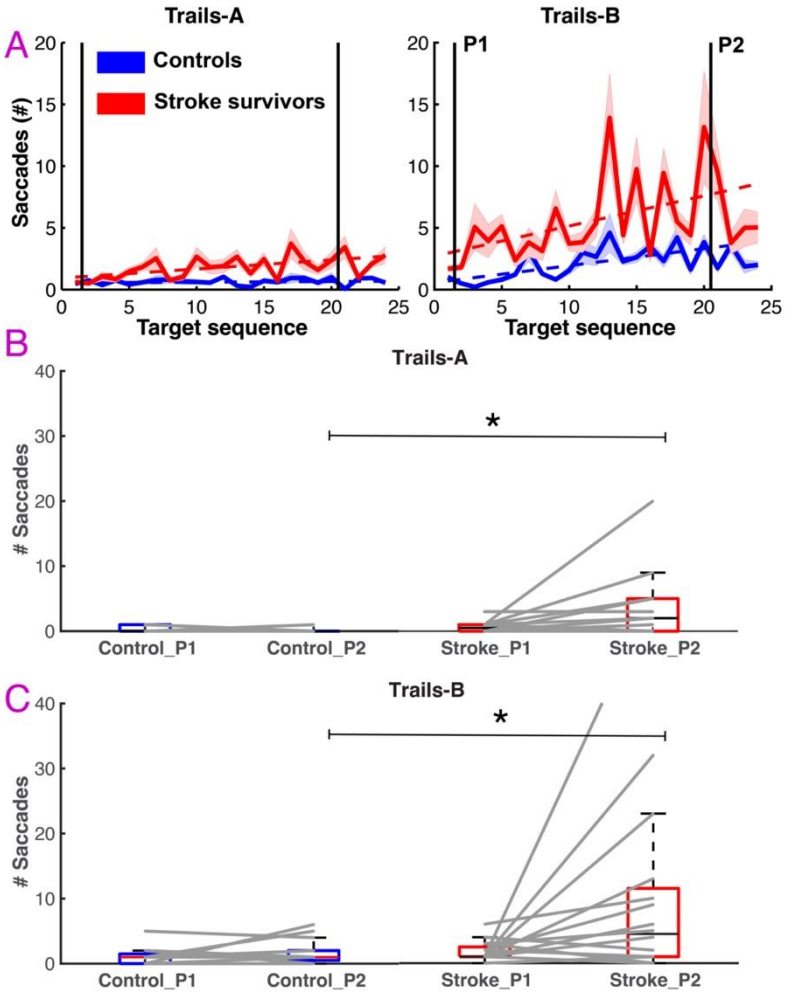

Figure 2: The number of saccadic eye movements increased as the Trails-B trial progressed. A) A regression model fit to the data between the first pair (P1) and last pair (P2) of targets shows no increase in number of saccades as the trial progressed in Trails-A. The number of saccades made per target increased for both controls and stroke survivors in Trails-B, but the regression slope was marginally steeper for stroke survivors. B) Boxplots for Trails-A shows that the stroke survivors made significantly more saccades than controls at the last target pair (P2). Stroke survivors also made more saccades at the last target pair (P2) than the first target pair (P1). C) Boxplot for Trails-B shows that both groups made more saccades at the last target pair (P2) than the first target pair (P1).

For Trails-B, mean fixation duration for the controls were 0.56±0.2 s and 1.62±0.3 s for the first and final pairs, respectively. For stroke survivors, the fixation durations were 1.04±0.3 s and 5.6±1.3 s, respectively. The intercept was higher for the stroke survivors (1.99, 95% interval [1.27,2.71]) than controls (0.98, 95% interval [10.68,1.29]). The slopes for the controls (0.06, 95% interval [0.03,0.08]) and stroke survivors were both positive, but marginally steeper for stroke survivors (0.12, 95% interval [0.06,0.18]). Our statistical model showed that the main effects for *group* ($p<0.001$, $\eta^2= 0.18$) and *pairs* ($p<0.001$, $\eta^2= 0.41$) were significant and so was the interaction effect ($p=0.017$, $\eta^2= 0.07$). Post-hoc tests showed significant differences between the two pairs for controls ($p=0.002$) and stroke

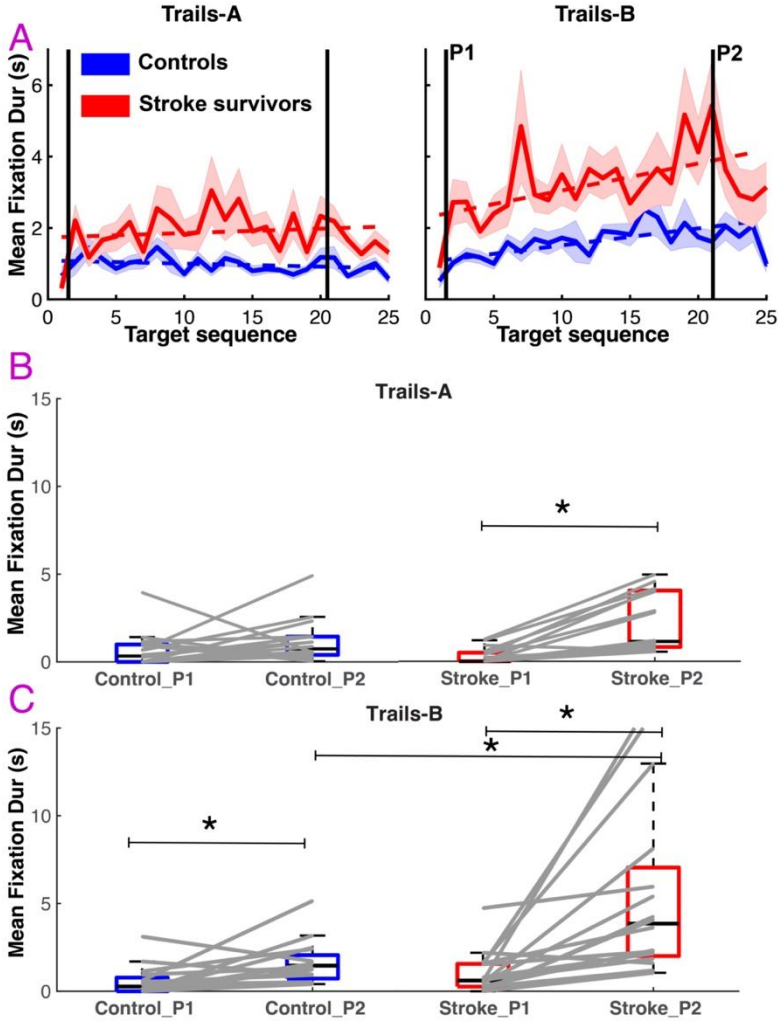

Figure 3: The mean fixation duration increased as the Trails-B trial progressed. A) A regression model fit to the data between the first target pair (P1) and last pair (P2) of targets shows no increase in mean fixation duration as the trial progressed in Trails-A. The mean fixation duration increased for both controls and stroke survivors in Trails-B, and again the regression slope was marginally steeper for stroke survivors suggesting they made longer fixations as the Trails-B trial progressed. B) Boxplots for Trails-A shows that the stroke survivors made significantly longer fixation than controls at the last target pair (P2). C) Boxplot for Trails-B shows that both groups made longer fixations at the last target pair (P2) than the first target pair (P1). Stroke survivors also made more saccades at the last target pair (P2) than the controls.

survivors ($p<0.001$) (Fig. 3C). The fixation duration was also significantly higher for the stroke survivors at the second pair ($p=0.005$). Together, these results suggest that both groups made longer fixations as the trial progressed in Trails-B, but stroke survivors made longer fixations than controls. Stroke survivors also made significantly longer fixations at the final pair in Trails-B. Bootstrap tests confirmed these results for both Trails-A and Trails-B.

The Mean Reach Speed (Fig. 4) results were more equivocal, as compared to the results on saccades and fixations. In Trails-A, the Mean Reach Speed (Fig. 4) for controls at the first target pair was 14.8±1.25 cm/s and for the last pair was 16.4±1.3 cm/s. For stroke survivors, the Mean Reach Speed was 13.1±1.7 cm/s and 11.5±1.6 cm/s, respectively. The regression intercepts were very similar between the two groups and the slopes were statistically indistinguishable from 0 (Fig. 4A). For Trails-A, the main effect of *group* was significant (p=0.025, η^2= 0.07). No other effects were significant and no post-hoc tests were significant (Fig. 4B). Together, these results suggest that the Mean Reach

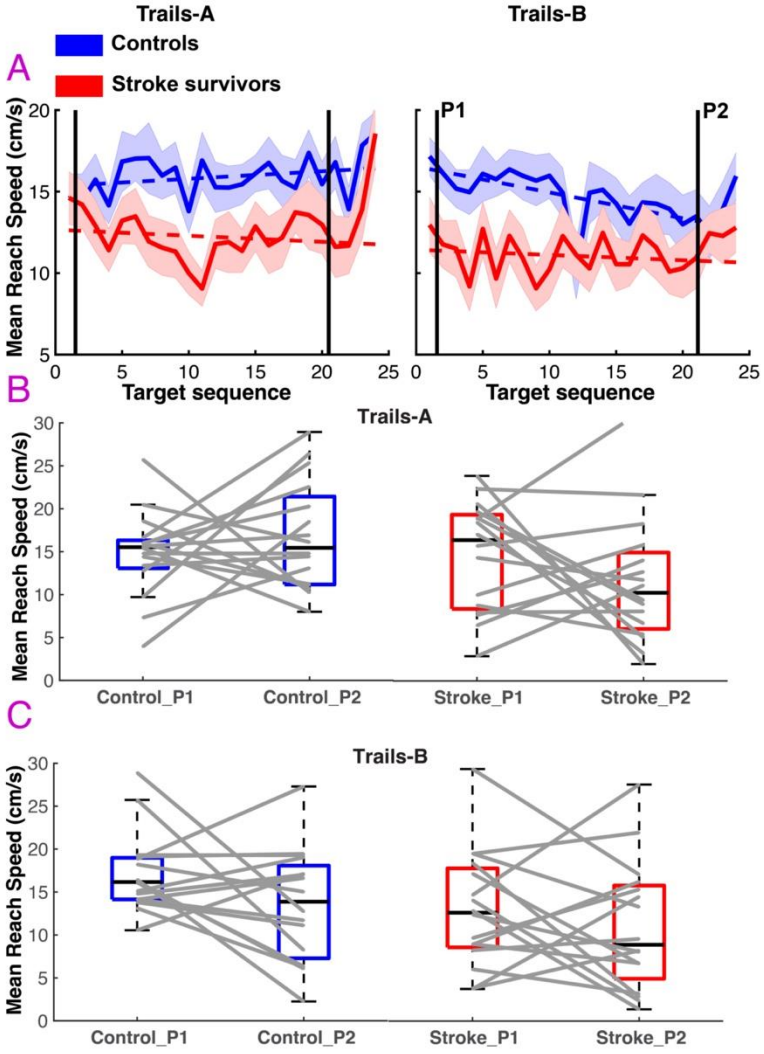

Figure 4: The mean reach speed appears to decrease for controls in Trails-B. A) A regression model fit to the data between the first target pair (P1) and last pair (P2) of targets shows no change in mean reach speed as the trial progressed in Trails-A. The mean reach speed appeared to decrease for both controls and stroke survivors in Trails-B, but the 95% confidence interval of the slope was negative only for the control group. In contrast, the intercepts were significantly lower for the stroke survivors in Trails-B, suggesting that the stroke survivors were overwhelmed with Trails-B throughout the entire task. B) Boxplots for Trails-A shows no significant differences. C) Boxplot for Trails-B shows no significant differences.

Speed was slower for the stroke survivors, but the speed did not change as the trial progressed for either group in Trails-A.

For Trails-B, the Mean Reach Speed for the first and final pair of targets for the controls were 15.3±1.3 cm/s and 12.5±2.23 cm/s, respectively. For stroke survivors, the Mean Reach Speed was

lower. For the first pair it was 11.3±1.9 cm/s and for the final pair, 7.4±1.98 cm/s. The intercept of the regression was significantly lower for stroke survivors (10.6, 95% interval [9.02,12.12]) than the controls (16.16, 95% interval [14.8,17.4]). The regression slope for controls was -0.16 (95% interval [-0.25, -0.06]). The slope for stroke survivors was statistically indistinguishable from 0 (Fig. 4A). The statistical model showed a main effect of *group* (p=0.027, η^2= 0.09) and *pairs* (p=0.035, η^2= 0.07). The post-hoc tests revealed no significant differences (Fig. 4C). Together, this suggests that the Mean Reach Speed for the stroke survivors was slower than the controls in Trails-B. The reaching speed decreased for the controls as the trial progressed, but not the stroke survivors. Overall, this analysis suggested incremental reductions in reaching speed as the trial progressed, suggesting that enhanced cognitive loading (as measured by the increase in the number of saccades and fixation durations) may have minimal impact on reaching movements.

We performed another analysis to test if saccades that occur during a reaching motion slow down reaching speed. We divided the reaching movements into two categories – one in which at least one or more saccades occurred during the movement, and those in which no saccades occurred during the movement. For Trails-A, when we compared these two reaching movements, we found no differences for both the groups (see Fig. 5A, upper panel). But for Trails-B, the reaching movements, where participants made saccades during a movement, were significantly slower (43%, p<0.001) for stroke survivors but not for controls (Fig. 5A, lower panel). We further confirmed that this difference was not due to a subset of the stroke survivors making an excessive number of saccades during reaching movements (Figs. 5B). We calculated the ratio of reaching movements made without saccades and compared the two groups (n=16 each) across both Trails-A and Trails-B. If only some stroke survivors were contributing to the Trails-B result, then we would expect to see those participants as a cluster closer to the top of the figure. We did not observe that. We also found no noteworthy differences between Trails-A and -B. This suggests that the higher number of saccades, which reflect increased cognitive loading during Trails-B, interfered with and slowed down reaching movements only in stroke survivors.

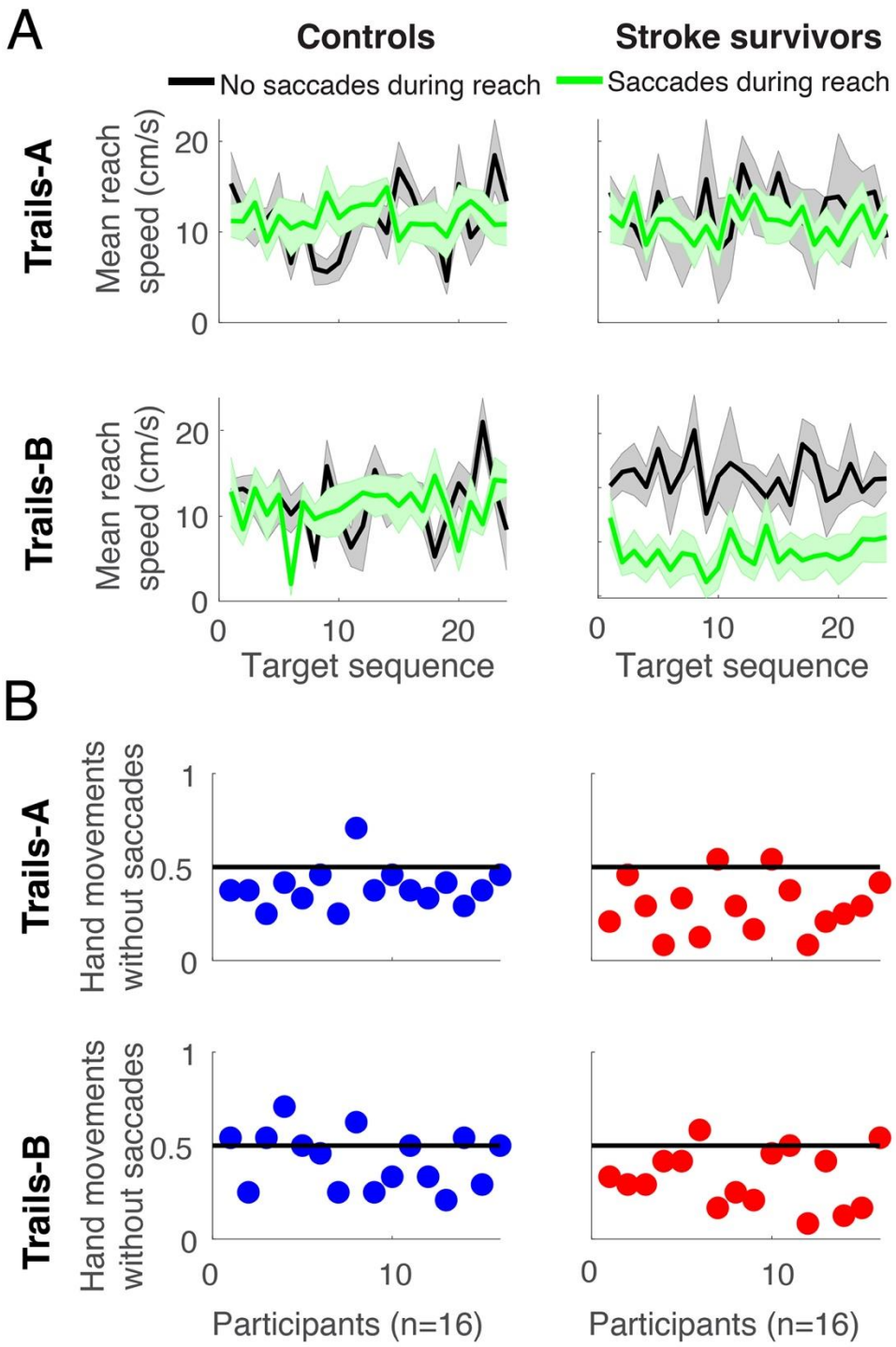

Figure 5: Saccades made during reaching movements slow down reaching speed in stroke survivors in Trails-B. A) We compared the speeds of reaching movements during which no saccade occurred and those movements in which at least one saccade occurred. There were no differences between the speeds of these movements in Trails-A for both groups. In Trails-B, for stroke survivors, the reaching movements during which at least one saccade was made was significantly slower. B) For each participant (n=16 in each group), we calculated the ratio of reaching movements in which no saccades were made. Here '0' indicates that at least one saccade was made during all the hand movements, and '1' indicates that no saccades were made during any of the reaching movements. This shows that all participants made at least one reaching movement with a saccade, but that there were no major differences between the two groups or tasks.

Discussion

Here, we addressed how eye movements may interfere with reaching movements during continuous tasks, such as the Trails-Making-Test. We first asked the question if the number of saccades increased as a trial progressed. Since Trails-B also involves task-switching and working memory, we predicted that the cognitive load would gradually increase in Trails-B as the participants progressed further along the alphanumeric sequence. This would cause participants to make more saccades and longer fixations. We also predicted that the increased saccades and longer fixations would slow down limb movements in both groups. Finally, we predicted the saccades to slow limb movements more in stroke survivors.

Overall, our results partially supported most of our predictions. Our main predictions were that as the Trails-B trial progressed, the increased cognitive load would cause more saccades, longer fixations, and slower limb movements. This would suggest a higher degree of eye-hand dyscoordination (EHdC). We found that the number of saccades and the mean fixation duration increased as the trial progressed for both groups. However, the overall impact of these increased saccades and longer fixations on reaching movements was minimal. Reaching speed did not slow down appreciably as the trial progressed.

Our final prediction was that EHdC would be stronger in stroke survivors, i.e., stroke survivors would make progressively more saccades and slower limb movements compared to healthy controls. Stroke survivors made more saccades and longer fixations in Trails-B, but their reaching speed, which was slower than the controls throughout the Trails-B trial (see Fig. 4), did not change significantly during the trial. However, we found that when stroke survivors made saccade(s) during a reaching movement in Trails-B, their reaching speed was slower than those reaching movements in which no saccades were made (Fig. 5A). Overall, this study provides evidence in favor of a stronger interference between eye and hand movements in stroke survivors when the cognitive load is high (Trails-B). Together, these results suggest that eye hand dyscoordination (EHdC) may be exacerbated in stroke survivors when they perform visuo-cognitive tasks with high cognitive load.

While an increase in eye movements has been documented in eye-hand tasks in chronic stroke survivors (Rizzo et al. 2017a; Rizzo et al. 2017b; Singh et al. 2017; Singh et al. 2018), the novel findings in the current study include the large number of saccades that stroke survivors made to already reached targets during in Trails-B. In contrast, controls did not make many more saccades to already reached targets (Fig. 2). We previously showed that in the Trails test, stroke survivors made more saccades than age-matched controls (Singh et al. 2017), and that these saccades caused less smooth and slower limb movements (Singh et al. 2018). Together, these findings suggest that top-down control of eye movements may be disrupted during visuo-cognitive tasks in stroke survivors (Noorani and Carpenter 2017).

Our findings also underscore a potential pathophysiological process that may underlie eye-hand dyscoordination (EHdC) with increasing cognitive demands in stroke survivors and controls. We posit that increased cognitive demands during visual search may disinhibit the ocular motor system (Rizzo et al. 2017b) and create downstream interference on limb movements, likely through pathways involving the basal ganglia (Carpenter 2002; Boehnke and Munoz 2008) (see Fig. 6). There is ample evidence to support that the prefrontal cortex is comprised of distinct networks involved in response inhibition, task-switching, and working memory (Miller and Cohen 2001). Competitive interactions between these networks may result in mutual inhibition, such that increased demands on task switching in Trails-B may interfere with response inhibition and working memory. The effects could include (1) disinhibition of eye movements and (2) difficulty using working memory to guide visual search. Furthermore, these excessive eye movements could overload the visual processing system.

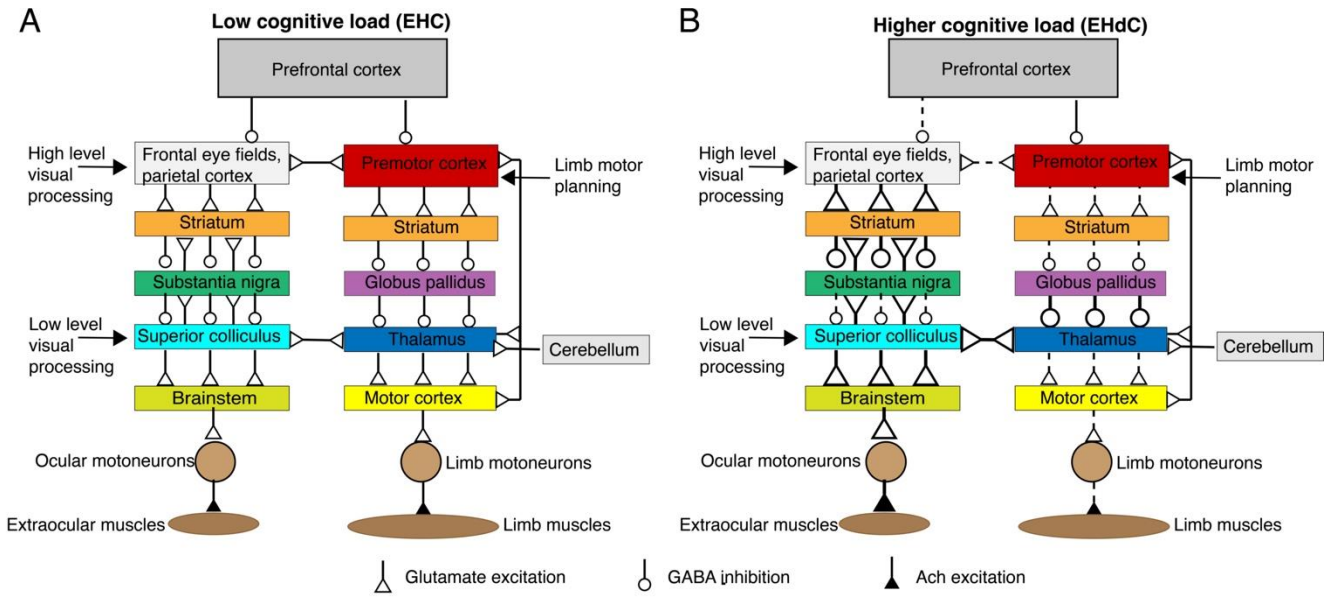

Figure 6: Proposed model for eye hand dyscoordination (EHdC) under enhanced cognitive load. Panel A shows the visual and ocular motor networks involved in eye movements (left) and limb movements (right) along with excitatory and inhibitory projections. The feedback projections within the visual system and interconnections between the visual, ocular motor, and limb motor systems are also shown. We propose that during enhanced cognitive loading, competitive interactions between prefrontal networks involved in response inhibition, task-switching, and working memory disinhibit the parietofrontal areas involved in ocular motor control. This increases the number of saccadic eye movements. The higher number of eye movements likely overload the visual system. This is supported by the longer fixation durations we observed in Trails-B as the task progressed. Then by changes in cortical and subcortical interactions between the ocular motor and limb motor systems, the motor system may also be inhibited during increased cognitive loading. Dashed lines indicate weakened projections and wider lines with larger arrow heads indicate stronger projections.

This could indirectly inhibit motor function through changes in cortical interactions between the parietofrontal visual networks, the premotor cortex, and the subcortical projections from the superior colliculus to the anterior thalamus and motor cortex (Boehnke and Munoz 2008).

Fixation duration is another sensitive marker of memory load and processing load, and, in fact, has been shown to be more sensitive than commonly used biomarkers, such as pupil size (Meghanathan et al. 2015). Fixation duration has not been well studied in stroke physiology. Herein, we clearly demonstrate large differences between control and stroke not only in total magnitude of duration, with stroke survivors increase the total length of a fixation up to 4-fold but also in the time course of the increases with fixational duration increasing over the course of the task in Trails-B. In visual search and free-viewing, it is generally well-established that fixational durations increase in length, as the searcher moves from a global to a more focused and local search strategy. This trend is typically observed over the first few seconds of visual search behavior (Unema et al. 2005). It has also been shown that in multi-target visual search, fixational durations generally increase with increasing memory load (Meghanathan et al. 2015). In the case of the Trails-test, a unique global to local strategy is required over a sequential multi-target task until all the numbers and/or letters are acquired. Fixation durational may indicate both the amount of information being processed and also the difficulty of future saccadic target selection (Pomplun et al. 2013).

Reaching speed was clearly different between controls and stroke survivors. It should be noted again that most stroke survivors used the ipsilesional limb (i.e., the less affected arm). Although some deficits in the ipsilesional limb have been documented (Schaefer et al. 2007; Semrau et al. 2017), leading to impaired motor function, the striking findings herein was the difference in reaching

speeds between those limb movements where saccade(s) occurred and those where none occurred. Previously, it has been demonstrated that stroke survivors made more saccades per reach if more impaired functionally (Fig. 4D in Singh et al. 2018) and that these saccades caused deficits in reaching control. Here we show evidence that these effects or decrements in performance are magnified when eye movements occur during limb movements during complex visuo-cognitive tasks.

During visually guided reaching, eye movements are coordinated in a synchronous manner with limb movements; however, the eye acquires the target well in advance of the limb and is typically anchored to the spatial target while the reach is completed (Neggers and Bekkering 2001). This suggests that saccadic suppression may, at least in part, minimize potential interference for other effectors, e.g., the limb. In fact, an entire sub-field in sports medicine is devoted to "quiet" eye or limiting eye movements during ongoing limb movements. Previous studies have clearly documented that saccadic programming can interfere with manual motor control depending on the feedback provided (Donkelaar et al. 2004). A simple yet appropriate comparison between eye-hand coordination, with the eye and hand viewed as independent effector systems, may be the walking-while-talking dual task paradigm that has been studied extensively in stroke survivors (Bowen et al. 2001). Concurrent performance of a cognitive task (talking) during a motor task (walking) typically leads to performance decrements because talking places additional demands on attentional resources, surpassing the capacity to process information used for walking. Although there are stark differences between walking-while-talking and eye-hand coordination, planning sequences of eye movements and brokering task switching in the Trails-test requires cognitive processes. Furthermore, eye movements that are decoupled from limb movements, as one might expect is occurring here given the dramatic increases in saccadic behavior, does have significant effects on the kinematics and trajectories of reaching (Gorbet and Sergio 2009).

Many clinical approaches fail to diagnose why patients with neurologic disease or injury struggle with many complex but essential activities of daily living (e.g., cooking, driving), but appear to retain typical function in simple motor tasks (e.g., reaching and pointing) (Yantz et al. 2010; Hird et al. 2015; Jaywant et al. 2018). These reports underscore the strong bi-directional relationship between the cognitive and motor systems that impact the ability to perform complex functional skills. Dual-task training can improve the ability to perform complex functional tasks by improving both cognitive and motor function (Fritz et al. 2015; Geroin et al. 2018; He et al. 2018). While the effectiveness of dual-task training has been shown in numerous studies, it is unclear how and why dual-task paradigms work. To that end, our work and proposed model (Fig. 6) could provide a mechanistic basis to probe interactions between top-down cognitive goals and bottom-up sensory processing for gaze and limb motor control.

Most of our stroke survivors performed the test with their non-dominant less-affected hand. In one study conducted in the subacute phase poststroke, we have shown that the less-affected arm exhibits minimal impairments in center-out reaching tasks (Semrau et al. 2017), but in the chronic phase, other studies have shown impairments in motor dexterity (Jebsen et al. 1971; Desrosiers et al. 1996) and coordination (Swinnen et al. 2002). Simple performance measures such as reaching movement speed of the less-affected arm, which are more pertinent to our study, have been shown to be similar between chronic stroke survivors and controls (Schaefer et al. 2007). Our results from Trails-A (Fig. 5A) support the results from the study by Schaefer and colleagues. The mean reach speed for stroke survivors and controls was similar for the two groups, regardless of whether saccadic eye movements were made or not during reaching movements. Furthermore, the mean reach speed was also similar between the two groups in Trails-B when no saccadic movements were made during the reaching actions (Fig. 5A). These results suggest that motor specific impairments of the less-

affected arm may not have played a huge role in slowing down those reaching movements in Trails-B (by approximately 40%) where participants also made saccades.

Our study also has some limitations. First, we had 4 females in our stroke group and 10 females in our control group. Worldwide, stroke is more common among men, but women are more severely affected by stroke (Haast et al. 2012). Ideally, we would have liked to check for sex-based differences between males and females amongst stroke survivors, but because of the skewed sex distribution in our groups we are unable to make any robust comparisons. Second, our experiment only allows us to provide correlational evidence to establish the directionality of the relationship between saccadic eye movements and slower reaching speeds. Based on our proposed model (Fig. 6), in future experiments, we would manipulate the size of the visual search field (no of targets), saliency of targets, increase motor demands (add background loads) etc. to probe how top-down task goals and bottom-up sensory processing interact for the control of gaze and limb movements.

In conclusion, here we showed that increased cognitive load in Trails-B (complex variant of the Trails-Making Test) caused stroke survivors to make more saccades and longer fixations as the trial progressed. Furthermore, we analyzed the reaching movements in which saccades were made and those in which no saccades were made separately. The reaching movements in which stroke survivors made saccades were about 40% slower than the ones in which no saccades were made. This was only observed for stroke survivors and in Trails-B. Together, this provides evidence for increased eye hand dyscoordination (EHdC) in stroke survivors during complex visuomotor tasks.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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