Functional Transcranial Doppler Ultrasound for Measurement of Hemispheric Lateralization During Visual Memory and Visual Search Cognitive Tasks

Benjamin Hage, Mohammed R. Alwatban, Erin Barney, Mark Mills, Michael D. Dodd, Edward J. Truemper, and Gregory R. Bashford, *Senior Member, IEEE*

***Abstract*— Functional transcranial Doppler ultrasound (fTCD) is a noninvasive sensing modality that measures cerebral blood flow velocity (CBFV) with high temporal resolution. CBFV change is correlated to changes in cerebral oxygen uptake, enabling fTCD to measure brain activity and lateralization with high accuracy. However, few studies have examined the relationship of CBFV change during visual search and visual memory tasks. Here a protocol to compare lateralization between these two similar cognitive tasks using fTCD is demonstrated. Ten healthy volunteers (age 21±2 years) were shown visual scenes on a computer and performed visual search and visual memory tasks while CBFV in the bilateral middle cerebral arteries was monitored with fTCD. Each subject completed 40 trials, consisting of baseline (25 s), calibration (variable), instruction (2.5 s), and task (20 s) epochs. Lateralization was computed for each task by calculating the bilateral CBFV envelope percent change from baseline and subtracting the right side from the left side. The results showed significant lateralization ($p < 0.001$) of the visual memory and visual search tasks, with memory reaching lateralization of 1.6% and search reaching lateralization of 0.5%, suggesting that search is more right lateralized (and therefore may be related to "holistic" or global perception) and memory is more left lateralized (and therefore may be related to local perception). This method could be used to compare cerebral activity for any related cognitive tasks as long as the same stimulus is used in all tasks. The protocol is straightforward and the equipment is inexpensive, introducing a low-cost high temporal resolution technique to further study lateralization of the brain.**

***Index Terms*— Biomedical engineering, biomedical imaging, biomedical signal processing, ultrasonic imaging, ultrasonography.**

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B. Hage and M. R. Alwatban are with the Department of Biological Systems Engineering, University of Nebraska–Lincoln, Lincoln, NE 68583 USA.

E. Barney is with the Yale Child Study Center, Yale School of Medicine, New Haven, CT 06510 USA.

M. Mills and M. D. Dodd are with the Department of Psychology, University of Nebraska–Lincoln, Lincoln, NE 68588 USA.

E. J. Truemper and G. R. Bashford are with the Department of Biological Systems Engineering, University of Nebraska–Lincoln, Lincoln, NE 68583 USA, and also with the Department of Pediatric Critical Care, Children's Hospital & Medical Center, Omaha, NE 68114 USA.

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I. Introduction

The relationship between neural activity and cerebral blood flow (CBF) has been known since at least 1928, when it was noted by Fulton [1]. Later studies have confirmed a close relationship between brain activity and blood flow [2]–[4]. CBF is regulated by the vasodilation and vasoconstriction of small cerebral arteries [5] and cerebral precapillaries and arterioles [6]. Currently, functional magnetic resonance imaging (MRI) is a popular technique used to measure hemodynamic changes that can be related to neural activation (see [7]–[9]), but this technique has the disadvantages of high cost and having limited time resolution for imaging transient changes in hemodynamics [10].

Aaslid *et al.* [11] described transcranial Doppler (TCD) ultrasound, a noninvasive method to measure CBF velocity (CBFV) in basilar cerebral arteries. Using this method, Aaslid [12] was able to show an increase in blood flow velocity in the posterior cerebral artery as a response to a visual stimulus. The linear relationship between relative changes in CBFV and CBF is valid, as long as there is no change in arterial diameter at the point of insonation [5], [12], [13]. While previous studies using MRI did not detect change in MCA diameter during hypocapnia or hypercapnia [13], recent studies using MRI show evidence contradicting this assumption and show a change in the MCA diameter during hypercapnia [14]–[16]. Therefore, if the MCA diameter changes under certain conditions, different approaches may be needed to measure neural activation accurately [16]. One such approach is lateralization, which is measured by comparing blood flow velocity in paired (left and right) cerebral arteries during the execution of specific cognitive tasks [17], [18]. Besides helping account for MCA diameter changes, lateralization provides the ability to differentiate between an increase in CBFV caused by stimuli and an increase caused by unrelated blood flow changes, for example, variations due to breathing [19].

Due to its low cost, simplicity, high temporal resolution, and safety, functional TCD (fTCD) ultrasound is useful for noninvasive investigation of functional lateralization in the brain. Studies show fTCD can provide very accurate information on neural activation and lateralization, for example, on verbal tasks [17]–[22], visuospatial tasks such as design comparison [22], mental rotation of figures [22], and perceptual speed, and visual discrimination tasks [23]. However, few studies have examined visual search [22] and visual memory [24], [25] cognitive tasks, and no studies have compared the two tasks to the best of the authors' knowledge. The purpose of this paper is to develop a standard procedure to compare two related cognitive tasks: visual search and visual memory, using fTCD.

II. Materials and Methods

A. Subjects

The subjects for this experiment consisted of ten volunteers (five males and five females), with an average age of 21.3 ± 1.8 years. All subjects were found to be right-handed using the Edinburgh inventory [26].

B. Transcranial Doppler

TCD ultrasound (DWL DopplerBox X, Compumedics Germany Gmbh) was used to collect bilateral blood flow velocity data. A fixation device was used to hold the transducers to the left and right transtemporal windows of the subjects [27]. The MCAs were insonated at depths between 43 and 55 mm, with Doppler gate size between 8 and 10 mm. The transducers were 2-MHz pulsed-wave transducers (Compumedics Germany Gmbh). Other transmit parameters are not reported by this commercial machine. The depth was initially set to expected depths for the MCA, based on published values [28], and the strongest signal was found by manual adjustment of the depth and transducer position. (The resulting depth ranged from 43 to 55 mm and gate size from 8 to 10 mm, with power set at 420 mW/cm^2.) Once the signal was optimized, the transducers were locked in place.

C. Experimental Setup and Procedure

Visual stimuli were displayed on a 19-in VGA monitor (85 Hz) at a viewing distance of 90 cm. Testing took place in a dimly lit sound attenuated testing room. The subject rested their head in a frame that kept their head steady. The subject was asked to look at visual scenes (Fig. 1) according to a previously published procedure [29]. Briefly, the subject was shown 40 visual scenes, corresponding to 40 trials, with each trial lasting approximately 47.5 s and consisting of four periods. Period I was a 25-s baseline period where the subject was shown a black screen. Period II was a calibration period where the subject was asked to fixate on a point on the center of a white screen, and then press the spacebar on a keyboard when they were ready to proceed (thus this period varied slightly in time length). Period III was a 2.5-s period in which cue words indicating the task to be performed were displayed on the screen: either "search for the N or Z" or "memorize the scene" was shown on a white background (tasks explained below). Period IV was a 20-s period in which the visual scene appeared on the screen and the subject performed the appropriate task. During the search task, the subject was told to search for a small "N" or "Z" hidden in the screen and to whisper the found letter after completion of the task; if they did not find it, they were asked to whisper a random letter. During the memory task, the subject was told to memorize the scene in preparation for a test that would be administered after the experiment (the test was not actually given). The tasks were given in a random order, and the same set of scenes was used for both search and memory tasks (the images were drawn randomly from the same pool of images, and thus each image had an equal probability of being viewed for either spatial or memory tasks, but no image was viewed more than once). The small letters "N" or "Z" were hidden so well in the scenes that it was very hard to find them without looking for them. The four periods occurred in the same order for every trial except the first trial, in which the calibration period occurred before the baseline period.

Fig. 1. Example of a visual scene used in the experiment. The subject was told either to search for a small "N" or "Z" hidden in the screen or to memorize the scene in preparation for a test that would be administered after the experiment.

D. Data Processing

Data from the DWL DopplerBox X were recorded and then exported for further analysis in MATLAB (R2014b v. 8.4.0, Mathworks, Natick, MA, USA). The fTCD data were recorded simultaneously on both the left and right MCAs and included the envelope waveform (the trace of the maximum velocities present in the Doppler spectrum at each point in time), systolic velocity (V_s, the maximum velocity present in the envelope waveform over one heartbeat cycle), diastolic velocity (V_d, the minimum velocity present in the envelope waveform over one heartbeat cycle), mean velocity (V_m, the average of the envelope waveform over one heartbeat cycle), Gosling's pulsatility index [$\mathrm{PI} = (V_s - V_d)/V_m$] [30], and Pourcelot's resistivity index ($\mathrm{RI} = (V_s - V_d)/V_s$, original reference [31]; see also [32]) for both directions (toward and away from the transducer). The PI and RI both capture information about resistance distal to the point being insonated [32]. The sampling frequency of the recorded data (i.e., the envelope waveform, V_s, V_d, V_m, PI, and RI values versus time) was 100 Hz. The positive envelope waveforms (denoting flow toward the transducer) were first filtered with a median filter of length five samples (corresponding to 50 ms), in order to remove spurious noise in the Doppler spectrum. Next, following [20], any samples were omitted from the envelope if the sample values were either greater than two times the truncated average (i.e., the average of all data except for the top and bottom 2.5% of values) of the entire filtered envelope for the experiment or less than 0.3 times the truncated average of the entire filtered envelope; differently from [20], all omitted samples were then replaced with the truncated average of the entire filtered envelope to avoid discarding data. One subject had less than 5% of samples in the left or right envelope replaced, and nine out of ten subjects had less than 1% replaced. The waveforms were then filtered with a smoothing low-pass filter (equiripple finite-impulse response filter, 189th order, 1-dB attenuation at 0.25 Hz and 40-dB attenuation at 1 Hz, filtered data corrected for time lag) using the function filter in MATLAB. Next, the start times of cue presentation periods (Period III of the experiment), provided by the software presenting the visual stimuli, were used to calculate the times at which the baseline time periods (Period I), cue time periods (Period III), and task time periods (Period IV) started and stopped (the fTCD recording and cue presentation start times were synchronized). The positive envelope waveforms for both sides of the subject were then divided into individual trials based on these starting and stopping times.

For both sides, the filtered positive envelope waveforms from all baseline periods (Period I) for memory and search tasks ($N = 40$) were averaged together, to get an average baseline period waveform lasting 25 s. For both sides, the filtered positive envelope waveforms from all memory task periods (Period IV) plus their preceding cue periods (Period III) were averaged together ($N = 20$) and the filtered positive envelope waveforms from all search task periods plus their preceding cue periods were averaged together ($N = 20$) separately, giving an average memory cue period + task period waveform and an average search cue period + task period waveform of 22.5 s each (2.5 s for cue period and 20 s for task period). For each subject, the average baseline period waveform and average cue period + task period waveform were joined to make up one average trial waveform for each subject and for each side. Period II (calibration) was omitted from this average trial waveform due to its variable time length.

The percent change from baseline, $dV_{\text{Left}}(t)$ or $dV_{\text{Right}}(t)$, for the left or right sides was then found as follows for both visual search and visual memory cognitive tasks [17], [19]–[21]:

$$dV_{\text{Left/Right}}(t)(\%) = 100\% * (V_{\text{Left/Right}}(t) - V_{\text{pre.mean,Left/Right}}) / V_{\text{pre.mean,Left/Right}} \quad (1)$$

where $V_{\text{Left/Right}}(t)$ is the waveform of the Doppler signal versus time for the left or right side after averaging over all 20 task periods and $V_{\text{pre.mean,Left/Right}}$ is the time average of the last 10 s of the average baseline waveform for the left or right side. The last 10 s of the average baseline waveform were used to find $V_{\text{pre.mean,Left/Right}}$ because it was the portion of the baseline period with the smallest standard deviation and it allowed subjects at least 15 s to recover from the previous task (other TCD studies have shown recovery times of more than 5 s but less than 10–20 s when recovering from elevated blood flow velocities to baseline levels after stimulus removal) [33], [34]. The time during which the cue word was displayed (Period III) was not included in calculating $V_{\text{pre.mean,Left/Right}}$ both because there was a visual stimulus present and also because anticipation of the task was likely to cause increased blood flow velocity [35].

The lateralization $\Delta V_{\text{Search}}(t)$ or $\Delta V_{\text{Memory}}(t)$ for the left and right sides was then found as follows [17], [19]–[21]:

$$\Delta V_{\text{Search(Memory)}}(t)(\%) = dV_{\text{Left}}(t)(\%) - dV_{\text{Right}}(t)(\%). \quad (2)$$

An example plot of $\Delta V_{\text{Search}}(t)$ and $\Delta V_{\text{Memory}}(t)$ versus time for one subject is shown in Fig. 2.

Finally, the ensemble averaged lateralization versus time was found for all ten subjects. The ensemble average $\Delta V_{\text{Memory}}(t)$ and $\Delta V_{\text{Search}}(t)$ versus time for memory and search tasks [see Figs. 3(b), 4(b), and 5] was found by averaging together all subjects' values of the lateralization $\Delta V_{\text{Memory}}(t)$ or $\Delta V_{\text{Search}}(t)$ sample by sample. To display the percent changes for the left and right sides $dV_{\text{Left}}(t)$ (%) and $dV_{\text{Right}}(t)$ (%) for search and memory, the values of $dV_{\text{Left}}(t)$ (%) and $dV_{\text{Right}}(t)$ (%) were averaged across all subjects sample by sample [see Figs. 3(a) and 4(a)].

For statistical analysis, at 5 s intervals during the task period, a two-tailed two-sample student's t-test with equal variances was performed on two sets of 50 consecutive points from the ensemble averaged $\Delta V_{\text{Memory}}(t)$ and $\Delta V_{\text{Search}}(t)$.

III. RESULTS

Fig. 3(a) shows ensemble average percent change versus time for left [$dV_{\text{Left,Search}}(t)$] and right [$dV_{\text{Right,Search}}(t)$] sides during the search task, and Fig. 3(b) shows ensemble average lateralization $\Delta V_{\text{Search}}(t)$ versus time for the search task. Fig. 4(a) shows ensemble average percent change versus time for left [$dV_{\text{Left,Memory}}(t)$] and right [$dV_{\text{Right,Memory}}(t)$] sides during the memory task, and Fig. 4(b) shows ensemble average lateralization $\Delta V_{\text{Memory}}(t)$ versus time for the memory task.

Fig. 5 shows the plots of ensemble average lateralization $\Delta V_{\text{Search}}(t)$ and $\Delta V_{\text{Memory}}(t)$ versus time, for comparison between the search and memory tasks. [The data shown in Fig. 5 are identical to the data from Figs. 3(b) and 4(b) combined.] On average, the memory task tended to have more positive values of lateralization than the search task, indicating that the memory task was more left lateralized, and the search task was more right lateralized. In Fig. 5, the ensemble average memory task lateralization $\Delta V_{\text{Memory}}(t)$ begins at about 0% before the cue word presentation period and remains constant until the beginning of the task period, when it begins to increase, and reaches a first maximum left lateralization of 1.6% about 7 s after the start of the task period. The value of $\Delta V_{\text{Memory}}(t)$ then decreases to about 1.3% at about 10 s after

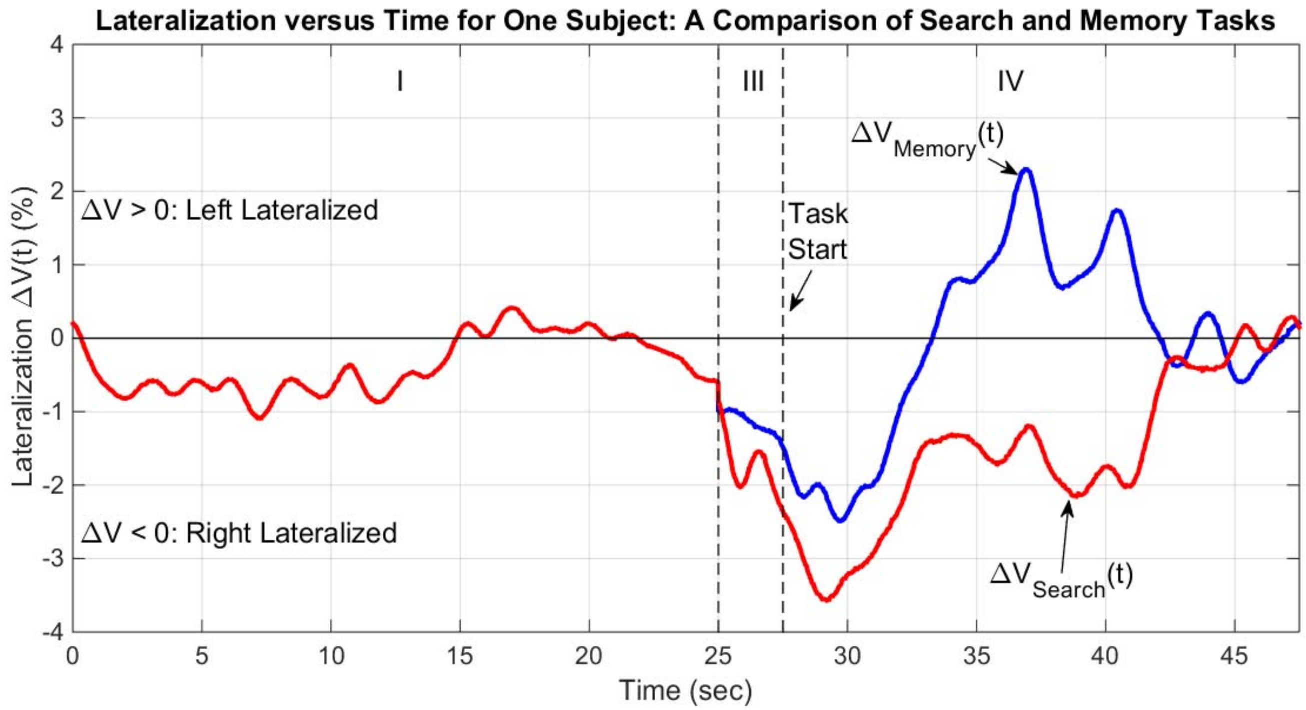

Fig. 2. Example plot of moving-window filtered $\Delta V_{\text{Search}}(t)$ and $\Delta V_{\text{Memory}}(t)$ versus time for one subject. Roman numerals I, III, and IV indicate time periods as described in text (Period II is not shown due to its variable time length between trials). The baseline period lateralization waveform is the same for both tasks, as baseline waveforms from the search and memory tasks were pooled when averaging.

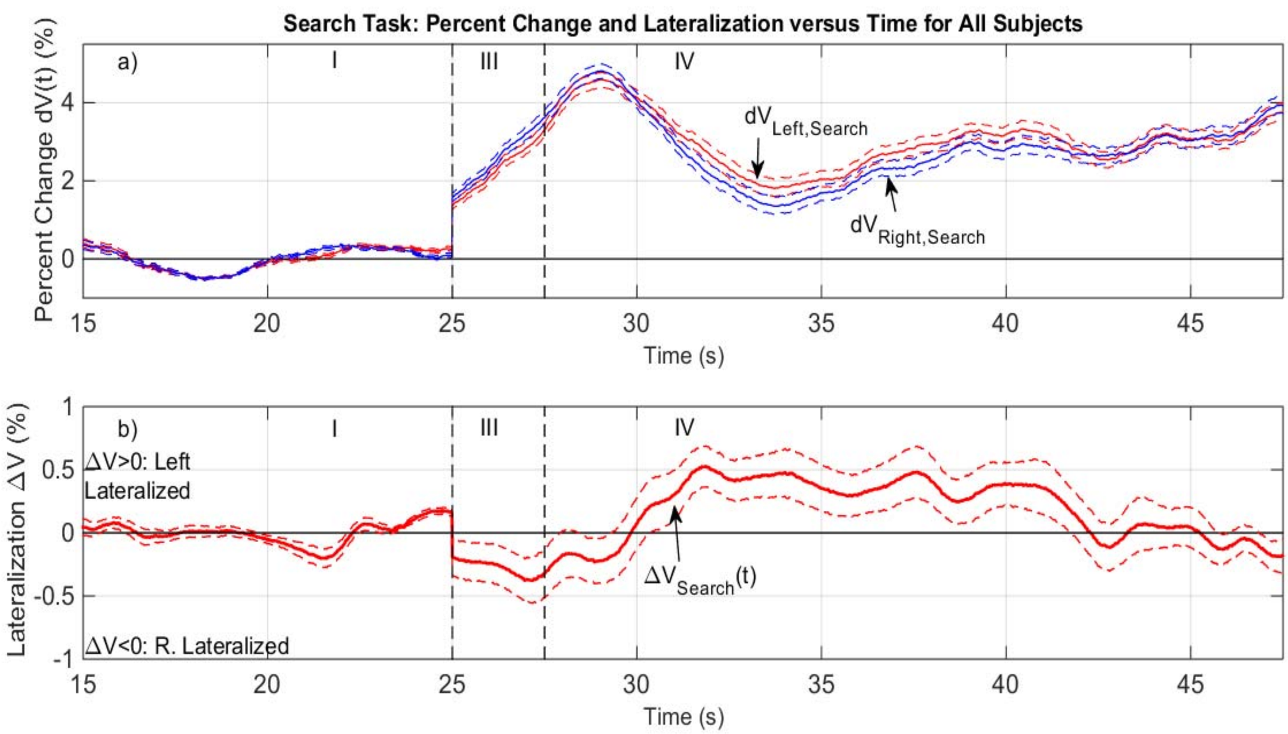

Fig. 3. (a) Percent change versus time for left [$dV_{\text{Left,Search}}(t)$] and right [$dV_{\text{Right,Search}}(t)$] sides during the search task (solid lines), averaged over all subjects. (b) Lateralization [$\Delta V_{\text{Search}}(t)$] versus time for all subjects for the search task (solid line), calculated using (2). Dashed lines above and below the solid lines represent ± 1 standard error of the mean. Roman numerals I, III, and IV indicate time periods as described in the text.

the start of the task period, and rises up to a second maximum of about 2.0% at about 14 s after the start of the task period before falling to 1.0% at the end of the task period.

In Fig. 5, the ensemble average search task lateralization $\Delta V_{\text{Search}}(t)$ begins at 0% before the cue period and becomes more right lateralized during the cue period, reaching

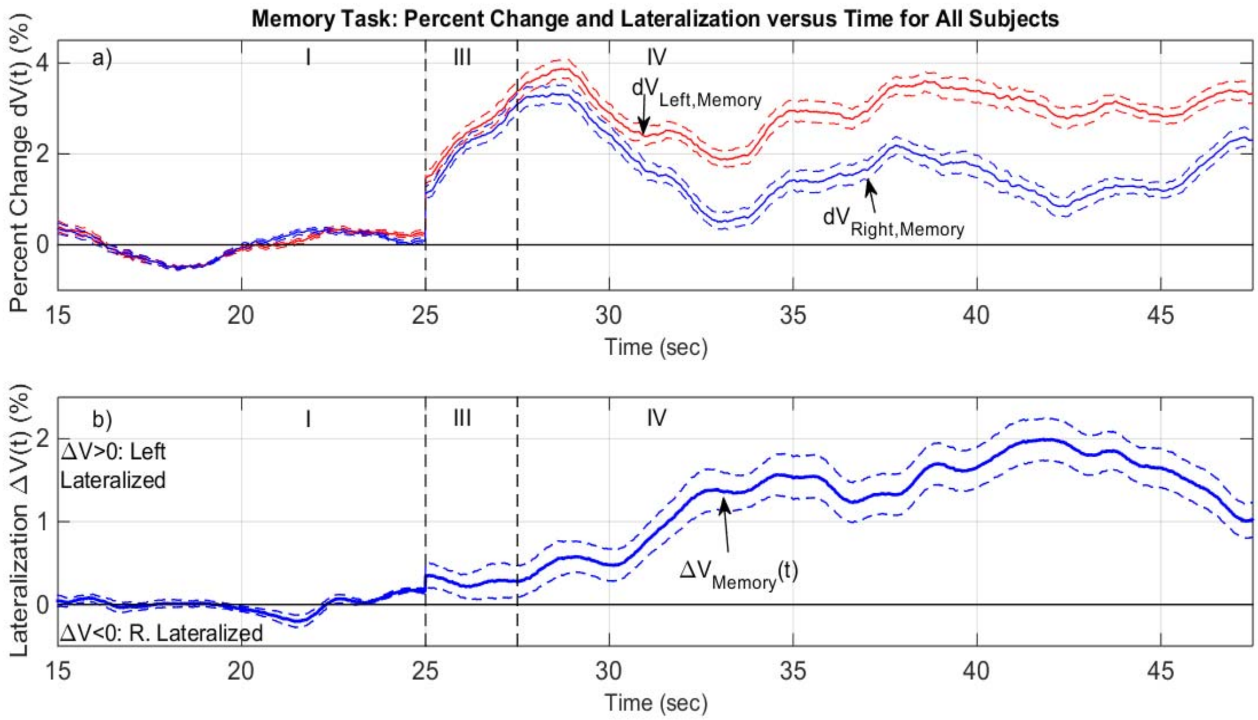

Fig. 4. (a) Percent change versus time for left [$dV_{\mathrm{Left,Memory}}(t)$] and right [$dV_{\mathrm{Right,Memory}}(t)$] sides during the memory task (solid lines), averaged over all subjects. (b) Lateralization [$\Delta V_{\mathrm{Memory}}(t)$] versus time for all subjects for the memory task (solid line), calculated using (2). Dashed lines above and below the solid lines represent ± 1 standard error of the mean. Roman numerals I, III, and IV indicate time periods as described in the text.

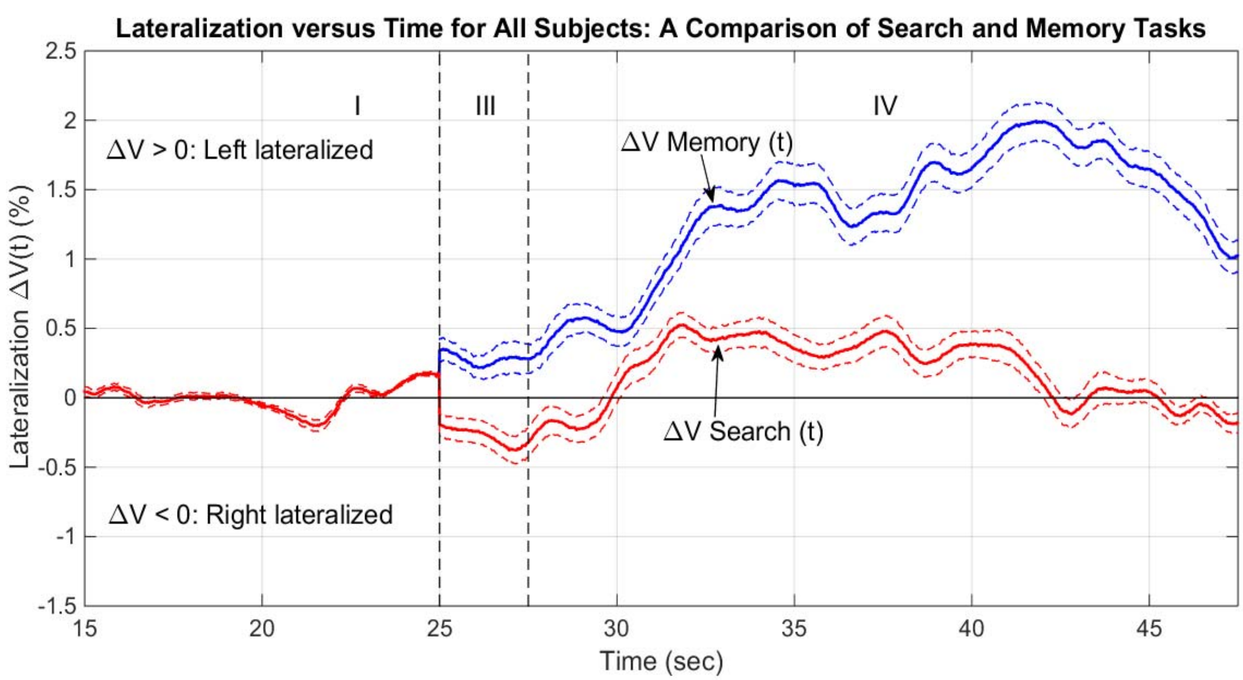

Fig. 5. Ensemble average lateralization $\Delta V_{\mathrm{Search}}(t)$ and $\Delta V_{\mathrm{Memory}}(t)$ versus time for search and memory tasks for all subjects (solid lines). Dashed lines above and below the solid lines represent ± 1 standard error of the mean. Roman numerals I, III, and IV indicate time periods as described in the text.

a maximum right lateralization of about -0.4% at approximately the start of the task period. The value of $\Delta V_{\mathrm{Search}}(t)$ then returns to 0% by about 2.5 s after the start of the task period and has a slight increase to 0.5% at 4 s after the start of the task period and remains at this level for about 9 s before returning to nearly 0% for the rest of the task period, indicating less hemispheric dominance overall during the search task than during the memory task.

For statistical analysis, at all times chosen except task period start (i.e., 5 s after task period start, 10 s after task period start, 15 s after task period start, and 20 s after task period start), the p-value was much less than 0.001, indicating a significant difference between the two sides.

IV. Discussion

This research possessed two novel features: 1) the application of fTCD to study the cognitive tasks of visual search and memory in the same study and 2) the use of identical stimuli for both tasks. In the first novel feature, lateralization and the amount of activation in each cerebral hemisphere over time were compared for visual search and visual memory cognitive tasks. The memory task tended to be more left lateralized overall, and the search task tended to be more right lateralized than memory. A possible explanation for this is that in the memory task, subjects may have tried to focus on details in a scene when memorizing it in preparation for a quiz to be given later (the left hemisphere is thought to play a role in local processing [36]); in the search task, subjects may have employed a strategy involving looking at the "big picture" in order to search as much of the picture as possible (the right hemisphere is thought to be involved in "global" or "holistic" processing [36], [37] and is known to play a role in visual search tasks [38]).

The second novel feature of the research was that the same set of visual scenes was used as stimuli for both cognitive tasks, allowing a direct comparison to be made between visual search and visual memory tasks without confounding variables between the two tasks. The procedure outlined above, e.g., comparing two similar cognitive tasks by finding the lateralization versus time for each task, provides a way to compare lateralization time courses between any two similar cognitive tasks that may be performed using the same set of visual stimuli. Some possible applications include comparing cognitive tasks such as viewing a visual scene with no specific instructions versus viewing a scene with instructions to assign a pleasantness rating to the scene, among others [29].

A possible confounding factor in the experimental procedure described is that subjects may not have all employed the same strategies during the tasks. For example, during the memory task, the subjects may have verbalized object names and locations, activating the left cerebral hemisphere [25].

V. Conclusion

An application of fTCD was presented for comparison of the lateralization of two related cognitive tasks. This modality is unique in its ability to display changes in lateralization with high temporal resolution. The TCD ultrasound data suggest that during visual search and visual memory tasks, there may be different patterns of lateralization versus time for CBF, suggesting different patterns of cerebral activation between the two tasks. Specifically, a difference in average lateralization over all participants between search and memory tasks was found to be significant by plotting the standard errors of the mean of the lateralization data versus time and by performing t-tests. Significantly, the same visual scenes were used as stimuli in both search and memory tasks, allowing a comparison to be made between average lateralization during search and tasks without the presence of confounding variables due to different experimental procedures for each task. Future work will involve examining patterns of lateralization versus time for left- and right-handed subjects separately, as well as the study of the time variation of other lateralized cognitive processes.

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Benjamin Hage received the B.S. and M.S. degrees in physics from the University of Nebraska–Lincoln, Lincoln, NE, USA, in 2009 and 2011, respectively, where he is currently pursuing the M.S. degree in biological systems engineering.

From 2009 to 2012, he was a Research Assistant with the Physics Department, University of Nebraska–Lincoln, where he volunteered with the Department of Chemistry from 2012 to 2013. Since 2013, he has been with the Biomedical Imaging and Biosignal Analysis Laboratory, Department of Biological Systems Engineering, University of Nebraska–Lincoln. His current research interests include medical ultrasound imaging and fluorescence microscopic imaging.

Mohammed R. Alwatban received the B.S. degree in biomedical technology from King Saud University, Riyadh, Saudi Arabia, and the M.S. degree in biomedical engineering from Wright State University, Dayton, OH, USA. He is currently pursuing the Ph.D. degree in biomedical engineering with the University of Nebraska–Lincoln, Lincoln, NE, USA.

He was a Biomedical Engineer at King Fahad Medical City, Riyadh, and a Biomedical Researcher at the Medical Research Center, King Abdullah International Medical Research Center, Riyadh. His current research interests include cerebrovascular reactivity, cerebral autoregulation, and using transcranial Doppler measurements as a biomarker of preclinical Alzheimer's disease.

Erin Barney received the B.S. degree in engineering science and psychology (valedictorian) from Trinity College, Hartford, CT, USA, in 2015.

She is currently completing a pre-doctoral fellowship at the Yale Child Study Center, New Haven, CT, USA, using eye tracking to characterize children on the autism spectrum. Her current research interests include child development, eye tracking, and developmental psychopathology.

Mark Mills received the B.A. degree in psychology from Oakland University, Rochester, MI, USA, and the Ph.D. degree in psychology from the University of Nebraska–Lincoln, Lincoln, NE, USA.

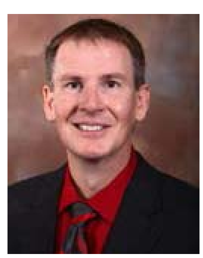
He is currently a Postdoctoral Fellow with the University of Toronto, Toronto, ON, Canada. His current research interests include scene perception, visual attention, and oculomotor control.

Michael D. Dodd received the B.S. degree in psychology from Trent University, Peterborough, ON, Canada, and the Ph.D. degree from the University of Toronto, Toronto, ON.

He was a Killam Postdoctoral Fellow at the University of British Colombia, Vancouver, BC, Canada, before joining the Psychology Faculty at the University of Nebraska–Lincoln, Lincoln, NE, USA, in 2007. He is a Cognitive Psychologist who conducts research, examining many facets of vision, attention, memory, and perception via a variety of different methodologies and technologies.

Edward J. Truemper received the B.S. degree in biology and the M.S. degree in microbiology, University of Mississippi, Oxford, MS, USA, and the M.D. degree from the University of Mississippi School of Medicine.

He completed his residency in Pediatrics at the University of Oklahoma, Norman, OK, USA, and a fellowship in Critical Care Medicine at the Baylor College of Medicine, Houston, TX, USA. He has applied transcranial Doppler to the management and investigation of children and young adults with brain injury since 1990. He is currently a Pediatric Intensivist at the Children's Hospital and Medical Center, Omaha, NE, USA, where he has been a chief collaborating investigator for more than 18 multiinstitutional studies over the past six years.



Gregory R. Bashford (M'96–SM'03) received the B.S. degree in electrical engineering from the University of Nebraska–Lincoln, Lincoln, NE, USA, and the Ph.D. degree in biomedical engineering from Duke University, Durham, NC, USA.

He was previously an Image Analysis Engineer at Acuson Corporation, Mountain View, CA, USA, Systems Engineer at GE Medical Systems, Milwaukee, WI, USA, and Senior Scientist at LI-COR Biosciences, Lincoln, NE, USA. In 2003, he joined the Faculty of the Biological Systems Engineering Department, University of Nebraska–Lincoln. His current research interests include methods and applications of blood flow measurement, especially transcranial Doppler for neurological protection, and musculoskeletal health assessment using ultrasound.