Cognitive difficulty intensifies age-related changes in anterior frontal hemodynamics:

Bierre, Kirstin; Lucas, Samuel; Guiney, Hayley; Cotter, J.D.; Machado, Liana

DOI:
10.1093/gerona/glw061

Cognitive Difficulty Intensifies Age-related Changes in Anterior Frontal Hemodynamics: Novel Evidence from Near-infrared Spectroscopy

Kirstin L. Bierre[1], Samuel J. E. Lucas[1,2], Hayley Guiney[1], James D. Cotter[1], Liana Machado[1]

University of Otago[1] and University of Birmingham[2]

Author Note

Kirstin L. Bierre, Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand; Samuel J. E. Lucas, School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, United Kingdom, and Department of Physiology, University of Otago, Dunedin, New Zealand; Hayley Guiney, Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand; James D. Cotter, School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand; Liana Machado, Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand.

This research was supported by the University of Otago. The authors thank Professor Jeff Miller and Bridget Forsyth for statistical advice, Tracy A. Cameron for technical advice, and Andrew Webb and Jared Laverty for assisting with computer programing.

Correspondence concerning this article should be addressed to Dr. Liana Machado, Department of Psychology, University of Otago, William James Building, 275 Leith Walk, Dunedin 9054, New Zealand. E-mail: liana@psy.otago.ac.nz

Abstract

Alongside age-related brain deterioration, cognitive functioning declines, particularly for more demanding tasks. Past research indicates that, to offset this decline, older adults exhibit hemodynamic changes consistent with recruitment of more anterior brain regions. However, the nature of the hemodynamic changes remains unclear. To address this knowledge gap, we used near-infrared spectroscopy in 36 young adults (aged 18-30) and 36 older adults (aged 60-72) to assess anterior frontal hemodynamic responses to engagement in three cognitive tasks of increasing difficulty. Behavioral results for all three tasks confirmed aging deficits (evidenced by slower reaction times and reduced accuracy rates) that progressively increased with task difficulty. Hemodynamic results showed opposing effects in young versus older adults, with oxygenated and total hemoglobin decreasing in young but increasing in older adults, particularly during the harder tasks. Also, tissue oxygenation increased only in older adults during the harder tasks. Among older adults only, anterior frontal hemodynamic changes correlated with better cognitive performance, indicating that they were compensatory in nature. These findings provide novel evidence of age-related anterior frontal hemodynamic changes that intensify with cognitive demands and compensate for performance deficits.

Key words: aging, cerebral hemodynamics, NIRS, task difficulty, inhibition, switching

Cognitive Difficulty Intensifies Age-related Changes in Anterior Frontal Hemodynamics: Novel Evidence from Near-infrared Spectroscopy

Healthy aging is associated with cognitive decline, which is evident for basic sensorimotor functioning, but most notable for more cognitively challenging tasks (1, 2). Age-related cognitive decline has been linked to brain changes that occur naturally with adult aging, including declines in prefrontal grey and white matter (3) and vascular function (4, 5). As the brain deteriorates with advancing age, remaining resources become insufficient to meet demand, particularly as cognitive difficulty increases (6).

A number of aging studies have shown evidence of hemodynamic changes in older adults that are thought to offset age-related deterioration of brain systems and the consequent cognitive decline (1). For example, functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) signals, which index the ratio of oxygenated hemoglobin (oxy-Hb) to deoxygenated hemoglobin (deoxy-Hb), suggest that during cognitive engagement older adults recruit more anterior frontal brain regions than young adults, including regions not activated in young adults, and this hemodynamic change in older adults has been linked to better performance (3). Given that increases in cognitive difficulty compound performance deficits in older adults, it makes sense to predict that increases in cognitive difficulty would also intensify age-related changes in hemodynamics, and indeed several fMRI studies have reported results in support of this notion (6). However, ratios of oxy-Hb to deoxy-Hb provide an incomplete picture of task-induced hemodynamic changes, and this limited information can be difficult to interpret across age groups due to age-related vascular changes (1, 7, 8). Furthermore, due to the bias of the fMRI BOLD signal toward deoxy-Hb (9), a change in deoxy-Hb can lead to a change in the BOLD signal even in the absence of a change in oxy-Hb (1).

The current study set out to provide a more complete characterization of the effects of advancing age on anterior frontal hemodynamic responses to cognitive task engagement, with a specific aim to test how cognitive task difficulty influences hemodynamic patterns in young versus older adults. To assess age-related changes, we compared a group of healthy young adults (aged 18-30 years) to a group of healthy older adults (aged 60-72 years). Cerebral hemodynamic responses to cognitive engagement were assessed bilaterally from the forehead using near-infrared spectroscopy (NIRS), which measured concentration changes in oxygenated hemoglobin (Δoxy-Hb) and deoxygenated hemoglobin (Δdeoxy-Hb), indicated blood volume changes based on their sum total (Δtotal-Hb), and calculated via spatially resolved spectroscopy tissue oxygenation changes based on the ratio of oxy-Hb to total-Hb (ΔTOI). Cognitive difficulty was manipulated across a set of three visuomotor tasks that were similar in terms of visual characteristics and motor requirements, but progressively increased in terms of executive cognitive demands, with the first task assessing basic visuomotor performance (Pro), the second task adding the need to impose inhibition (Anti), and the third task adding the need to switch between tasks (Pro/Anti) (10, 11).

A previous study involving these cognitive tasks in young women showed that all three tasks elicited reductions from resting baseline in oxy-Hb, deoxy-Hb, and total-Hb in the region of right anterior frontal cortex underlying the forehead, and only Δdeoxy-Hb depended on the task (10). The reductions in Δtotal-Hb indicate that the young women recruited blood to more posterior brain regions, and the progressive decrease in Δdeoxy-Hb across the tasks indicates sensitivity to increasing task demands, despite no increase in blood flow into the area (as indicated by the reductions in Δoxy-Hb and Δtotal-Hb during engagement in all three tasks). Thus, replication of the cognitive method and NIRS recording site used in Cameron et al. (10) provided the opportunity in the current study to test whether cognitive tasks that elicit Δoxy-Hb and Δtotal-Hb reductions in young adults instead elicit increases in older adults,

and moreover whether increases in task difficulty intensify the age-related changes in hemodynamic patterns. Based on past studies, we expected that older adults would exhibit poorer performance especially as task difficulty increased, and that this would be associated with increases in Δoxy-Hb in anterior frontal brain regions. The key novel contributions of the current study relate to simultaneously characterizing changes in oxy-Hb, deoxy-Hb, total-Hb, and tissue oxygenation in the sampled region, thus providing a more detailed hemodynamic characterization. By including three tasks that systematically varied in cognitive difficulty, changes in the NIRS values could be considered across active conditions (from Pro to Anti and from Anti to Pro/Anti) rather than relying solely on changes from resting baseline, which can be difficult to interpret if resting baseline states differ between the two age groups (8). Moreover, this design allowed consideration of within-group changes in the NIRS values across the tasks (i.e., cognitive difficulty levels), rather than relying solely on between-group comparisons, which can be difficult to interpret due to other age-related vascular changes (1). To determine whether age-related changes in hemodynamic patterns afforded compensation for cognitive deficits, we tested whether task-induced hemodynamic changes predicted cognitive performance.

Method

The University of Otago Human Ethics Committee approved this study prior to its commencement, and all participants gave informed written consent prior to taking part. Experimental sessions took 1.5-2 hr; participants were encouraged to take rest breaks between cognitive tasks.

Participants

The participants reported here included 36 young adults (16 males, 32 right handed) recruited at the University of Otago and 36 older adults (16 males, 32 right handed) recruited from the local community. Five additional young adults and three additional older adults

were excluded due to technical difficulties with the NIRS recordings; these participants will not be mentioned further. The two age groups were matched for sex and handedness. All participants were reimbursed NZ$20-25. All participants reported having normal or corrected to normal visual acuity, no color blindness, and no neurological or psychiatric history.

Materials and Procedure

Surveys and Cognitive Test Familiarization. All participants first completed the Beck Depression Inventory-II (BDI-II) (12), were verbally administered the Pittsburgh Sleep Quality Index (PSQI) (13), and reported their years of education to enable consideration of whether depression, sleep quality, and education influenced the pattern of results, given previously established interrelationships between depression, sleep, education and cognitive performance (14-17). To screen for dementia, only the older adults then completed the Mini-Mental State Examination (MMSE) (18). All older adults scored at least 26 out of 30 on the MMSE, which indicates none were demented. Then, all participants completed the cognitive tests to familiarize themselves with the tasks prior to data collection.

Cerebrovascular Setup. Participants were then fitted with a near-infrared spectrometer (NIRO-200, Hamamatsu Photonics K.K., Hamamatsu, Japan), which recorded at a frequency of 1 Hz relative concentrations of oxy-Hb, deoxy-Hb, and their sum total (total-Hb), using a modified Beer-Lambert Law. Total oxygenation index (TOI = oxy-Hb / total-Hb × 100) was calculated by the NIRS system (spatially resolved spectroscopy method) from the light attenuation slope along the distance from the emitting point as detected by two photodiodes in the detection probe. The methodology of this system has been described previously (19, 20). Emitter-to-detector distance was 4.5 cm. The optodes were secured to the left and right sides of the forehead as high up and as laterally as possible to avoid the frontal sinus area while also avoiding contact with the hairline in an effort to prevent melanin pigmentation within the hair from interfering with the infrared light

transmission (21). The optodes were held in a light proof holder and secured on the skin with tape that further prevented light entering.

Cerebrovascular and Cognitive Testing. During data collection, participants sat in a dimly lit room 57 cm from a computer monitor displaying a black background with their chins on a chinrest (Applied Science Laboratories, Bedford, MA). First, hemoglobin data were recorded for 2 min while participants sat still and focused on a black monitor; the second minute of this recording served as baseline. Then, hemoglobin data were recorded while participants completed three cognitive tests in a fixed order: Pro, Anti, and then Pro/Anti (see Figure 1).

The cognitive tests were programmed using MATLAB (The MathWorks, Natick, MA) and The Psychophysics Toolbox (22, 23). Stimuli appeared on a black background and participants responded using a two-button DirectIN Response Box (Empirisoft, New York; see Figure 1). The trial sequence was identical across the three tests. Each trial began with the appearance of a 0.3° white fixation dot centered on the computer monitor. After a variable interval of 400, 600, 800, 1000 or 1200 ms, a 2° square appeared 8° to the left or right of the center of the monitor (measured to the center of the square). For the first test (Pro), the square was always green and participants were instructed to respond by pressing the button on the same side as the square. For the second test (Anti), the square was always red and participants were instructed to respond by pressing the button on the opposite side of the square. For the third test (Pro/Anti), the trials from the Pro and Anti tests were randomly intermixed, thus the square was either green or red, and participants were instructed to respond by pressing the button on the same side as green squares and on the opposite side of red squares. For all three tests, participants were instructed to use their index fingers to press the appropriate button as fast as they could without compromising accuracy. An error tone sounded for 300 ms and the trial was marked as incorrect if the participant pressed the wrong button or responded in less

than 100 ms or greater than 1500 ms after the square appeared. RTs and accuracy were recorded. The screen went blank for 500 ms between trials. The duration of the fixation period and the side of the square were randomized across trials, with the constraint that each combination of conditions occurred equally often. Participants completed four practice then 20 test Pro trials, six practice then 20 test Anti trials, and six practice then 40 test Pro/Anti trials.

Statistical Analyses

Independent *t* tests determined whether years of education, depression (BDI-II) or sleep quality (PSQI) differed significantly between young and older adults. For any significant differences, analyses of covariance (ANCOVA) were run to allow for statistical control of the covariate.

For each participant, cognitive performance during each of the three tasks was calculated using median correct RTs and percentage correct during the test trials. NIRS measures (Δoxy-Hb, Δdeoxy-Hb, Δtotal-Hb, and ΔTOI) were calculated using the mean change from baseline during completion of the test trials of each of the three cognitive tasks. Normality of each dataset was determined using the Shapiro-Wilk test. For non-normally distributed data, non-parametric tests were used to back up parametric results.

Initial analysis of all cognitive and NIRS data was carried out using a mixed analysis of variance (ANOVA). In cases where homogeneity of covariances was not present, the mixed ANOVA was still run and the results reported. Significant interactions were followed up with independent *t* tests for the between-subjects variable of age group and repeated-measures ANOVAs with Bonferroni-adjusted post hoc analyses for the within-subjects variable of task. In cases where sphericity was violated ($p < .05$), either a Greenhouse-Giesser (when $\varepsilon < .75$) or Huynh-Feldt (when $\varepsilon \geq .75$) correction was applied. Pearson's

correlations were used to determine if age-related hemodynamic changes were associated with better cognitive performance.

Results

Table 1 summarizes the participant characteristics and results for the indices of cognitive performance (RTs and percentage correct) and hemodynamic changes (Δoxy-Hb, Δdeoxy-Hb, Δtotal-Hb, and ΔTOI).

Covariates

BDI-II scores, which estimated depressive symptoms during the 2 weeks prior to participation, indicated minimal depression (0-13) in 86.1% of the young adults and 94.4% of the older adults, mild depression (14-19) in 5.6% of the young adults and 5.6% of the older adults, and moderate depression (20-28) in 8.3% of the young adults. PSQI scores, which estimated sleep quality during the month prior to participation, indicated good sleep quality (0-5) in 72.2% of the young adults and 58.3% of the older adults, and poor sleep quality (6-21) in 27.8% of the young adults and 41.7% of the older adults. Young adults completed more years of education than older adults, $t(51.979) = 3.106$, $p = .003$, $d = .73$, but the groups did not differ in BDI-II scores, $t(59.905) = 1.278$, $p = .206$, $d = .30$, or PSQI scores, $t(70) = -.977$, $p = .332$, $d = .23$.

Cognitive Performance

A mixed ANOVA, with age group as a between-participants variable and task (Pro, Anti, or Pro/Anti) as a within-participants variable, revealed main effects of age group for both RTs, $F(1, 70) = 89.309$, $p < .001$, $\eta_p^2 = .561$, and accuracy rates, $F(1, 70) = 17.353$, $p < .001$, $\eta_p^2 = .199$, as well as main effects of task for both RTs, $F(2, 140) = 591.739$, $p < .001$, $\eta_p^2 = .894$, and accuracy rates, $F(1.764, 123.492) = 21.512$, $p < .001$, $\eta_p^2 = .235$. In addition, age group interacted with task for both RTs, $F(2, 140) = 52.135$, $p < .001$, $\eta_p^2 = .427$, and

accuracy rates, $F(1.764, 123.492) = 5.914$, $p = .005$, $\eta_p^2 = .078$, reflecting increased differences between the age groups as task demands increased. Analysis of log-transformed RTs showed that the interaction remained significant ($p < .001$). The subsections below report analyses that followed up the age group by cognitive task interactions.

Aging Effects. Independent *t* tests analyzed aging effects for each cognitive task. The results revealed that older adults exhibited significantly slower RTs than younger adults on the Pro task, $t(70) = -4.444$, $p < .001$, $d = 1.05$, Anti task, $t(70) = -6.985$, $p < .001$, $d = 1.65$, and Pro/Anti task, $t(70) = -10.819$, $p < .001$, $d = 2.55$. In addition, older adults exhibited significantly lower accuracy than younger adults on the Anti task, $t(56.123) = 2.504$, $p = .015$ $d = .59$, and Pro/Anti task, $t(70) = 3.543$, $p = .001$, $d = .83$. After adjustment for years of education, using ANCOVA, the age-group differences remained for RTs ($p < .001$ for all three tasks) and for accuracy ($p \leq .020$ for the Anti and Pro/Anti tasks), which indicates that the group difference in education does not explain the group differences in cognitive performance. As the RT and percentage correct data were not normally distributed, non-parametric Mann-Whitney *U* tests were also run, which yielded results consistent with the parametric findings. In addition, analysis of log-transformed RTs ruled out a generalized slowing account for the age-group differences as all group differences remained significant ($p < .001$ for all three tasks).

Task Effects. Repeated-measures ANOVA analyzed within each age group the influence of increasing task difficulty on RTs and accuracy. The results confirmed that as difficulty increased across the tasks (from Pro to Anti to Pro/Anti), RTs and accuracy changed in both young and older adults. Post hoc analyses confirmed that RTs increased significantly in both age groups from the Pro to Anti task (young adults: $M = 42$ ms, 95% CI [12, 72], $p = .003$; older adults: $M = 122$ ms, 95% CI [89, 154], $p < .001$) and from the Anti to Pro/Anti task (young adults: $M = 161$ ms, 95% CI [131, 192], $p < .001$; older adults: $M = 261$

ms, 95% CI [231, 291], $p < .001$), whilst accuracy decreased significantly only from the Anti to Pro/Anti task (young adults: $M = -1.92\%$, 95% CI [-3.59, -0.24], $p = .021$; older adults: $M = -4.17\%$, 95% CI [-7.35, -0.98], $p = .007$). As the RT and percentage correct data were not normally distributed, non-parametric Friedman tests were also run, which yielded results consistent with the parametric findings.

NIRS

Figures 1-3 illustrate in each age group anterior frontal hemodynamic changes during engagement in each of the cognitive tasks relative to resting baseline. An initial ANOVA of each of the NIRS measures, with age group as a between-participants variable and task (Pro, Anti, or Pro/Anti) and hemisphere as within participant variables, failed to detect any significant main effects of or interactions with hemisphere ($p > .1$) for any of the NIRS measures except a main effect of hemisphere for ΔTOI, $F(1,70) = 8.426$, $p = .005$, $\eta_p^2 = .107$. Thus in subsequent analyses the NIRS data for Δoxy-Hb, Δdeoxy-Hb, and Δtotal-Hb were collapsed across hemispheres, whilst ΔTOI was analyzed by hemisphere. Importantly, initially ANOVA revealed main effects of age group for Δoxy-Hb, $F(1, 70) = 10.225$, $p = .002$, $\eta_p^2 = .127$; and Δtotal-Hb, $F(1, 70) = 10.636$, $p = .002$, $\eta_p^2 = .132$; as well as main effects of task for Δoxy-Hb, $F(2, 140) = 17.597$, $p < .001$, $\eta_p^2 = .201$; Δdeoxy-Hb, $F(1.598, 111.858) = 61.453$, $p < .001$, $\eta_p^2 = .467$; and ΔTOI, $F(2, 140) = 17.836$, $p < .001$, $\eta_p^2 = .203$. Moreover, age group interacted with task for Δoxy-Hb, $F(2, 140) = 7.045$, $p = .001$, $\eta_p^2 = .091$; Δdeoxy-Hb, $F(1.598, 111.858) = 4.929$, $p = .014$, $\eta_p^2 = .066$; Δtotal-Hb, $F(2, 140) = 5.216$, $p = .007$, $\eta_p^2 = .069$; and ΔTOI, $F(2, 140) = 11.078$, $p < .001$, $\eta_p^2 = .137$. These findings are consistent with age-related increases in anterior frontal activation (as indexed by these hemodynamic changes) as task demands increased. The subsections below report follow-up analyses for the age group by cognitive task interactions.

Aging Effects. Independent *t* tests analyzed aging effects for each cognitive task. The results revealed that older adults exhibited significantly higher levels of Δoxy-Hb and Δtotal-Hb than young adults during all three tasks: Pro task [Δoxy-Hb: $t(70) = -2.104$, $p = .039$, $d = .50$; Δtotal-Hb: $t(70) = -2.361$, $p = .021$, $d = .56$], Anti task [Δoxy-Hb: $t(70) = -2.585$, $p = .012$, $d = .61$; Δtotal-Hb: $t(70) = -2.822$, $p = .006$, $d =. 67$], and Pro/Anti task [Δoxy-Hb: $t(70) = -4.213$, $p < .001$, $d = .99$; Δtotal-Hb: $t(70) = -3.926$, $p < .001$, $d = .93$]. After adjustment for years of education, using ANCOVA, the age-group differences remained significant ($p < .04$) for Δoxy-Hb and Δtotal-Hb for all tasks, except for Δoxy-Hb during the Pro task which no longer showed a significant age-group difference ($p = .100$). This indicates that, disregarding Δoxy-Hb during the easiest task, the group difference in education does not explain the group differences in NIRS values. The two age groups did not significantly differ in Δdeoxy-Hb or ΔTOI (left or right hemisphere) during any of the three tasks ($p > .08$). As the majority of the NIRS data in older adults and the ΔTOI data in the young adults were not normally distributed, non-parametric Mann-Whitney *U* tests were also run, which yielded results consistent with the parametric findings with the addition of significant age-group differences detected for Δdeoxy-Hb and ΔTOI in the left hemisphere for the Pro/Anti task and for ΔTOI in the right hemisphere for all three tasks. Although the NIRS system used here can quantify only change from a baseline (not absolute concentrations of hemoglobin) (24), and thus the baseline values should not be interpreted on their own, to aid interpretation of the change values we describe the relative baseline values in the two age groups. Resting baseline values in the older compared to young adults were higher for oxy-Hb ($p = .111$), total-Hb ($p = .821$), and TOI ($p = .007$ in the left hemisphere, $p = .033$ in the right hemisphere), and lower for deoxy-Hb ($p = .012$). Thus, the higher Δoxy-Hb and Δtotal-Hb in the older adults cannot be attributed to lower baseline values, as the baseline values were non-significantly higher in the older adults.

Task Effects. Repeated-measures ANOVA analyzed within each age group the influence of increasing task difficulty on the NIRS data. In the older adults, results showed main effects of task for Δoxy-Hb, Δdeoxy-Hb, Δtotal-Hb, and ΔTOI. Post hoc analyses confirmed that older adults' Δoxy-Hb increased significantly from the Pro to Anti task, M = 6.78 µM/l, 95% CI [1.08, 12.47], p = .015; and the Anti to Pro/Anti task, M = 12.16 µM/l, 95% CI [5.22, 19.11], p < .001; while older adults' Δdeoxy-Hb decreased significantly from the Pro to Anti task, M = -3.09 µM/l, 95% CI [-5.19, -0.99], p = .002; and the Anti to Pro/Anti task, M = -7.44 µM/l, 95% CI [-10.08, -4.80], p < .001. Post hoc analyses also revealed that older adults' ΔTOI increased significantly from the Anti to Pro/Anti task for both the left hemisphere, M = 0.46%, 95% CI [0.22, 0.71], p < .001; and right hemisphere, M = 0.61%, 95% CI [0.32, 0.89], p < .001. In contrast, older adults' ΔTOI did not significantly increase from the Pro to Anti task for either hemisphere (p > .08), nor did Δtotal-Hb significantly increase from the Pro to Anti task or the Anti to Pro/Anti task (p > .06). As the majority of the NIRS data in older adults were not normally distributed, non-parametric Friedman tests were also run, which showed results consistent with the parametric findings. In the young adults, increased task demands were associated only with changes in Δdeoxy-Hb; post hoc analyses confirmed that Δdeoxy-Hb significantly decreased significantly from the Pro to Anti task, M = -2.99 µM/l, 95% CI [-5.27, -0.72], p = .006; and the Anti to Pro/Anti task, M = -3.31 µM/l, 95% CI [-5.63, -0.98], p = .003.

Correlations

To elucidate whether hemodynamic changes were associated with cognitive performance, correlation analyses were run for each NIRS measure and each cognitive performance measure. In the older adults, the results revealed during the easiest task (Pro) a moderate positive correlation between the cognitive accuracy rate measure and ΔTOI in the right hemisphere, $r(34)$ = .356, p = .033; and during the most difficult task (Pro/Anti)

moderate negative correlations between the cognitive RT measure and both Δoxy-Hb, $r(34) = -.335$, $p = .046$, and Δtotal-Hb, $r(34) = -.421$, $p = .011$. Results in older adults also revealed moderate negative correlations trending towards significance between the cognitive accuracy rate measure and Δdeoxy-Hb during the Pro task, $r(34) = -.322$, $p = .056$; and between the cognitive RT measure and Δoxy-Hb during the Anti task, $r(34) = -.311$, $p = .065$. All of these correlations are consistent with the hemodynamic changes supporting better performance in older adults. No other correlations between cognitive performance and NIRS measures were detected in young or older adults ($p > .1$).

Discussion

The current research aimed to provide a more complete characterization of the effects of advancing age on anterior frontal hemodynamic responses (measured from the forehead) to cognitive task engagement, and more specifically the influence of increasing cognitive task difficulty. As expected based on past findings, the behavioral results showed for all tasks aging deficits (evidenced by slower RTs and reduced accuracy rates) that progressively increased with task difficulty. Hemodynamic results in the young adults replicated the patterns reported in Cameron et al. (10); namely, Δoxy-Hb, Δdeoxy-Hb, and Δtotal-Hb all exhibited negative values (i.e., reduced hemoglobin concentrations relative to resting baseline), and only Δdeoxy-Hb varied with task difficulty. In contrast, older adults showed increases in Δoxy-Hb, Δtotal-Hb, and ΔTOI, along with the expected decreases in Δdeoxy-Hb, especially as task difficulty increased. These age-group specific patterns of task-induced hemodynamic changes provide novel evidence in support of claims that older adults recruit more anterior brain regions than young adults, particularly as cognitive demands increase. Furthermore, in the older adults, correlations between the NIRS and cognitive performance measures indicate that the hemodynamic changes support better performance, thus providing partial compensation for cognitive deficits.

The replication of the hemodynamic patterns reported in young women in Cameron et al. (10) in the current sex-mixed young adult group provides confirmation that the far anterior frontal region underlying the forehead does not play an active role in the visuomotor tasks utilized. As reviewed in Cameron et al. (10), the negative change in total-Hb during each of the tasks suggests that task engagement caused blood to be recruited to more posterior brain regions. These reductions from resting baseline cannot be accounted for by a high baseline specific to the young adults as total-Hb baseline values did not differ across the two age groups ($p > .8$, and contrary to this account, young adults had a numerically lower total-Hb baseline). Moreover, in contrast to the older adults, neither Δoxy-Hb nor Δtotal-Hb increased significantly across the tasks in the young adults. The lack of increases in oxy-Hb and total-Hb across the tasks confirms that young adults did not progressively recruit anterior frontal regions underlying the forehead.

Of particular interest are the hemodynamic results obtained in the older adults, which support previous claims that recruitment of more anterior brain regions increases with cognitive task difficulty, and further that the age-specific hemodynamic changes aid cognitive performance (6). However, unlike previous research that relied on fMRI-based oxy-Hb-to-deoxy-Hb ratios, the current experiment used NIRS, which showed that older adults' Δoxy-Hb, Δtotal-Hb, and ΔTOI all increased with cognitive demands, thus indicating increases in blood volume and cerebral oxygenation. These results demonstrate the clearest evidence, to our knowledge, that as task difficulty increases, older adults recruit progressively anterior brain regions not recruited in young adults. The correlations with cognitive performance indicate that this additional recruitment likely reflects an attempt to cope with cognitive deficits, which presumably stem from age-related deterioration of brain systems rendering available neural resources insufficient to satisfy task demands, especially as cognitive difficulty increases (6). By utilizing NIRS, we were able to go beyond previous studies and

show that better task performance was associated with higher Δoxy-Hb, Δtotal-Hb, and ΔTOI, thus providing novel evidence indicating that increases in blood volume and cerebral oxygenation in the anterior frontal lobe underpin successful compensatory performance in older adults.

A previous NIRS aging study reported distinct hemodynamic patterns in young versus older adults during engagement in a modified Stroop task with a task difficulty manipulation that, similar to the current study, involved adding the need to inhibit or switch between tasks (25). However, the nature of the distinct hemodynamic patterns differed from our study in that, during the most difficult task, oxy-Hb in young adults increased but older adults showed limited evidence of an increase (see Figure 2 in 25). Given that older adults show far greater automaticity of word reading than young adults (26), the stark differences in the nature of the age-related hemodynamic changes between the studies could relate to the use of word stimuli in Laguë-Beauvais et al. (25) versus non-word stimuli in the current study, although it should be noted that other methodological differences could have also contributed to differences in the results (e.g., in their study switch trials were cued 500 ms before target onset, whereas in our study switches occurred unpredictably and thus participants could not prepare in advance for the switch).

The design employed here has several advantages that address methodological concerns discussed in the literature regarding making comparisons between age groups, given the physiological vascular changes that occur with advancing age (27, 28). First, separate quantification of oxy-Hb and deoxy-Hb concentrations provides a more detailed characterization of hemodynamic responses to cognitive task engagement that helps circumvent concerns about the ambiguous nature of the BOLD signal used in fMRI studies (1, 8). Due to advancing age affecting oxygen metabolism rates, oxy-Hb-to-deoxy-Hb ratios can be higher in the absence of higher neuronal activity or cerebral blood flow, thus leaving

the cause of a stronger BOLD signal unclear (7, 28, 29). Although the current study did not measure oxygen metabolism rates, quantification of both Δoxy-Hb and Δdeoxy-Hb enabled the determination of whether oxy-Hb increases occurred in association with concomitant blood volume (total-Hb) increases, thus discounting reduced oxygen metabolism as the source of the changes (reduced oxygen metabolism rates could account for increased oxy-Hb and TOI and decreased deoxy-Hb, but not increased total-Hb). Second, consideration of hemoglobin changes across cognitive tasks helps circumvent concerns about group differences in the baseline condition (8). While group differences for a given cognitive task could reflect differences at baseline (e.g., if one group shows lower resting state values, a similar magnitude vascular response to cognitive engagement could yield a greater change value in the group with lower resting values), group differences in the patterns of change across tasks are impervious to group differences in baseline states. Thus, in the current study, the group-specific effects of increased cognitive difficulty across tasks (i.e., Anti compared to Pro, and Pro/Anti compared to Anti) cannot be accounted for by baseline group differences. Moreover, the group differences in Δoxy-Hb and Δtotal-Hb were not accompanied by group differences in baseline values for these variables, and in both cases the direction of non-significant differences opposed a baseline-difference account (i.e., the higher Δoxy-Hb and Δtotal-Hb in older adults cannot be attributed to lower baseline values as older adults exhibited numerically higher oxy-Hb and total-Hb baseline values).

Although our study has revealed intriguing novel findings, several limitations are worthy of note. First, we cannot conclude a causal link, as this would require a longitudinal design. Second, our study did not assess oxygen metabolism rates, which are known to change with adult aging (1), and thus we cannot comment on differences between the age groups or on how oxygen metabolism rates changed across the cognitive tasks. Given that increases in cerebral blood flow (indicated by increased oxy- and total-Hb in the current

study) normally occur in association with increased oxygen metabolism rates, and vice versa (30, 31), oxygen metabolism rates presumably decreased in the young adults and increased in the older adults in the anterior frontal region sampled, but the current data cannot confirm this. A future study could combine NIRS with transcranial Doppler ultrasound, as per Yang et al. (31), to allow simultaneous measurement of oxygen metabolism rates. Third, our study did not assess neurovascular coupling, which adult aging is known to compromise (32), thus we cannot comment on how differences in neurovascular coupling may have influenced the results; however, compromised neurovascular coupling could not produce the pattern of results reported here (of note, the increases in oxy-Hb, total-Hb, and TOI in the older adult group are at odds with reduced neurovascular coupling). Fourth, our NIRS data relate only to far anterior frontal regions, and thus we cannot comment on the brain regions functionally relevant in young adults. By simultaneously recording from more posterior frontal regions, future research can determine whether young versus older adults exhibit distinct hemodynamic patterns in brain regions activated in young adults. Such a study could also characterize age-related changes in hemispheric asymmetries, which previous research has indicated may be an important aspect of compensatory hemodynamic changes (3, 25). In light of previously established links between physical activity habits and maintenance of higher concentrations of oxy-Hb in anterior frontal cortex (10), a future exercise intervention study in older adults may be worthwhile to test whether increased physical activity levels might augment the hemodynamic changes and related cognitive benefits, thus further abating age-related cognitive decline.

In conclusion, notwithstanding the limitations discussed above, the current research indicates that during engagement in the cognitive tasks tested here older adults recruited anterior frontal brain regions not activated in young adults, as indicated by changes in oxy-Hb, blood volume (total-Hb) and cerebral oxygenation (TOI). The distinct hemodynamic

patterns exhibited by older adults not only intensified with increasing cognitive demands but also appear to support cognitive performance that helps counteract aging deficits, as indicated by correlations between the NIRS and cognitive measures in the older adults. These findings converge with and extend prior research reporting age-related changes in anterior frontal hemodynamics.

References

1. Chen PL, Machado L. Age-related deficits in voluntary control over saccadic eye movements: Consideration of electrical brain stimulation as a therapeutic strategy. Neurobiol Aging. 2016. doi:10.1016/j.neurobiolaging.2016.02.010
2. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med. 2013;**29**:737-752. doi:10.1016/j.cger.2013.07.002
3. Cabeza R, Dennis NA. Frontal lobes and aging: deterioration and compensation. In: Stuss DT, Knight RT, eds. Principles of frontal lobe function. 2nd ed. New York: Oxford University Press; 2012:628-652.
4. Warsch JR, Wright CB. The aging mind: vascular health in normal cognitive aging. J Am Geriatr Soc. 2010;**58 Suppl 2**:S319-324. doi:10.1111/j.1532-5415.2010.02983.x
5. Deak F, Freeman WM, Ungvari Z, Csiszar A, Sonntag WE. Recent Developments in Understanding Brain Aging: Implications for Alzheimer's Disease and Vascular Cognitive Impairment. J Gerontol A Biol Sci Med Sci. 2016;**71**:13-20. doi:10.1093/gerona/glv206
6. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. J Gerontol B Psychol Sci Soc Sci. 2010;**65**:405-415. doi:10.1093/geronb/gbq035
7. Kar K, Wright J. Probing the mechanisms underlying the mitigation of cognitive aging with anodal transcranial direct current stimulation. J Neurophysiol. 2014;**111**:1397-1399. doi:10.1152/jn.00736.2013
8. Gauthier CJ, Madjar C, Desjardins-Crepeau L, Bellec P, Bherer L, Hoge RD. Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging. Neurobiol Aging. 2013;**34**:1469-1485. doi:10.1016/j.neurobiolaging.2012.11.002
9. Steinbrink J, Villringer A, Kempf F, Haux D, Boden S, Obrig H. Illuminating the BOLD signal: combined fMRI-fNIRS studies. Magn Reson Imaging. 2006;**24**:495-505. doi:10.1016/j.mri.2005.12.034
10. Cameron TA, Lucas SJ, Machado L. Near-infrared spectroscopy reveals link between chronic physical activity and anterior frontal oxygenated hemoglobin in healthy young women. Psychophysiology. 2015;**52**:609-617. doi:10.1111/psyp.12394
11. Guiney H, Lucas SJ, Cotter JD, Machado L. Evidence cerebral blood-flow regulation mediates exercise-cognition links in healthy young adults. Neuropsychology. 2015;**29**:1-9. doi:10.1037/neu0000124
12. Beck A, Steer R, Brown G. *Manual for Beck Depression Inventory-II (BDI-II)*. San Antonio, TX: Psychology Corporation; 1996.
13. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;**28**:193-213. doi:10.1016/0165-1781(89)90047-4
14. Benitez A, Gunstad J. Poor Sleep Quality Diminishes Cognitive Functioning Independent of Depression and Anxiety in Healthy Young Adults. Clin Neuropsychol. 2012;**26**:214-223. doi:10.1080/13854046.2012.658439
15. Sutter C, Zöllig J, Allemand M, Martin M. Sleep Quality and Cognitive Function in Healthy Old Age: The Moderating Role of Subclinical Depression. Neuropsychology. 2012;**26**:768-775. doi:10.1037/a0030033
16. Yaffe K, Peltz CB, Ewing SK, McCulloch CE, Cummings SR, Cauley JA*, et al.* Long-term Cognitive Trajectories and Mortality in Older Women. J Gerontol A Biol Sci Med Sci. 2016. doi:10.1093/gerona/glw003
17. Goveas JS, Rapp SR, Hogan PE, Driscoll I, Tindle HA, Smith JC*, et al.* Predictors of Optimal Cognitive Aging in 80+ Women: The Women's Health Initiative Memory Study. J Gerontol A Biol Sci Med Sci. 2016;**71 Suppl 1**:S62-71. doi:10.1093/gerona/glv055
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;**12**:189.

19. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke. 2001;**32**:2492.
20. Lucas SJ, Ainslie PN, Murrell CJ, Thomas KN, Franz EA, Cotter JD. Effect of age on exercise-induced alterations in cognitive executive function: relationship to cerebral perfusion. Exp Gerontol. 2012;**47**:541-551. doi:10.1016/j.exger.2011.12.002
21. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth. 2009;**103 Suppl 1**:i3-13. doi:10.1093/bja/aep299
22. Brainard DH. The Psychophysics Toolbox. Spat Vis. 1997;**10**:433-436.
23. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat Vis. 1997;**10**:437-442.
24. Ekkekakis P. Illuminating the black box: investigating prefrontal cortical hemodynamics during exercise with near-infrared spectroscopy. J Sport Exerc Psychol. 2009;**31**:505-553.
25. Laguë-Beauvais M, Brunet J, Gagnon L, Lesage F, Bherer L. A fNIRS investigation of switching and inhibition during the modified Stroop task in younger and older adults. Neuroimage. 2013;**64**:485-495. doi:10.1016/j.neuroimage.2012.09.042
26. Lien MC, Allen PA, Ruthruff E, Grabbe J, McCann RS, Remington RW. Visual word recognition without central attention: evidence for greater automaticity with advancing age. Psychol Aging. 2006;**21**:431-447. doi:10.1037/0882-7974.21.3.431
27. Lu H, Xu F, Rodrigue KM, Kennedy KM, Cheng Y, Flicker B*, et al.* Alterations in cerebral metabolic rate and blood supply across the adult lifespan. Cereb Cortex. 2011;**21**:1426-1434. doi:10.1093/cercor/bhq224
28. Hutchison JL, Lu H, Rypma B. Neural mechanisms of age-related slowing: the DeltaCBF/DeltaCMRO2 ratio mediates age-differences in BOLD signal and human performance. Cereb Cortex. 2013;**23**:2337-2346. doi:10.1093/cercor/bhs233
29. Mohtasib RS, Lumley G, Goodwin JA, Emsley HC, Sluming V, Parkes LM. Calibrated fMRI during a cognitive Stroop task reveals reduced metabolic response with increasing age. Neuroimage. 2012;**59**:1143-1151. doi:10.1016/j.neuroimage.2011.07.092
30. D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci. 2003;**4**:863-872. doi:10.1038/nrn1246
31. Yang R, Brugniaux J, Dhaliwal H, Beaudin AE, Eliasziw M, Poulin MJ*, et al.* Studying cerebral hemodynamics and metabolism using simultaneous near-infrared spectroscopy and transcranial Doppler ultrasound: a hyperventilation and caffeine study. Physiol Rep. 2015;**3**. doi:10.14814/phy2.12378
32. Flück D, Beaudin AE, Steinback CD, Kumarpillai G, Shobha N, McCreary CR*, et al.* Effects of aging on the association between cerebrovascular responses to visual stimulation, hypercapnia and arterial stiffness. Front Physiol. 2014;**5**:49. doi:10.3389/fphys.2014.00049

Table 1 *Summary of participant characteristics, indices of cognitive performance and hemodynamic changes, and age differences*

	Young Adults (n = 36)			Older Adults (n = 36)			Age Differences			
Variable	*M*	*SD*	Range/[95% *CI*]	*M*	*SD*	Range/[95% *CI*]	*M*	*p-value*		95% *CI*
Age (years)	21.9	2.7	18-30	66.2	3.8	60-72	44.2	**<.001**	*	[42.67, 45.77]
Education (years)	15.4	1.6	13-20	13.7	3.1	8-18	-1.8	**.003**	*	[-2.93, -0.63]
Beck Depression Inventory-II	6.9	6.7	0-25	5.3	4.3	0-16	-1.7	**.206**		[-4.35, 0.96]
Pittsburgh Sleep Quality Index	4.7	2.8	0-13	5.3	2.5	1-11	0.6	**.332**		[-0.64, 1.86]
Mini-Mental State Examination				29.4	0.9	26-30				
Pro reaction times (ms)	341	50	[326, 359]	393	50	[377, 409]	52	<.001	*†	[29, 76]
Anti reaction times (ms)	383	61	[365, 405]	515	96	[487, 547]	132	<.001	*†	[94, 170]
Pro/Anti reaction times (ms)	544	92	[516, 576]	776	89	[748, 805]	232	<.001	*†	[189, 274]
Pro accuracy (% correct)	98.89	2.11	[98.06, 99.58]	99.03	2.34	[98.19, 99.72]	0.14	.792		[-0.91,1.19]
Anti accuracy(% correct)	99.03	2.34	[98.19, 99.72]	97.08	4.03	[95.69, 98.33]	-1.94	.015	*†	[-3.50, -0.39]
Pro/Anti accuracy (% correct)	97.11	3.50	[95.94, 98.17]	92.92	6.19	[90.70, 94.89]	-4.19	.001	*†	[-6.56, -1.83]
Δoxy-Hb Pro (μM/l)	-8.30	21.80	[-15.37, -.64]	4.72	30.07	[-4.30, 14.87]	13.02	.039	*†	[0.68, 25.37]
Δoxy-Hb Anti (μM/l)	-5.09	26.14	[-13.29, 4.58]	11.50	28.27	[2.63, 20.71]	16.59	.012	*†	[3.79, 29.39]
Δoxy-Hb Pro/Anti (μM/l)	-3.72	28.60	[-12.84, 6.44]	23.66	26.49	[15.22, 31.80]	27.37	**<.001**	*	[14.41, 40.33]
Δdeoxy-Hb Pro (μM/l)	-3.39	8.01	[-5.87, -.67]	-4.51	13.68	[-8.75, -.13]	-1.13	.670		[-6.40, 4.14]
Δdeoxy-Hb Anti (μM/l)	-6.38	10.64	[-9.84, -2.72]	-7.60	14.80	[-12.04, -2.85]	-1.22	.688		[-7.29, 4.83]
Δdeoxy-Hb Pro/Anti (μM/l)	-9.69	11.95	[-13.72, -5.78]	-15.04	14.04	[-19.15, -10.33]	-5.36	.086	†	[-11.49, 0.77]
Δtotal-Hb Pro (μM/l)	-12.20	21.61	[-19.17, -4.18]	0.41	23.67	[-6.79, 8.31]	12.61	.021	*†	[1.96, 23.26]
Δtotal-Hb Anti (μM/l)	-11.43	23.77	[-18.53, -3.27]	4.21	23.26	[-3.36, 12.22]	15.64	.006	*†	[4.58, 26.69]
Δtotal-Hb Pro/Anti (μM/l)	-13.42	26.42	[-21.28, -4.75]	9.70	23.48	[2.08, 17.55]	23.12	**<.001**	*	[11.38, 34.87]
ΔTOI left Pro (%)	0.27	3.80	[-.72, 1.67]	-0.07	1.14	[-.45, .28]	-0.34	.612		[-1.66, 0.98]
ΔTOI right Pro (%)	0.50	3.16	[-.21, 1.68]	0.39	1.25	[-.03, .80]	-0.11	.849	†	[-1.24, 1.02]
ΔTOI left Anti (%)	0.38	3.80	[-.57, 1.82]	0.01	1.18	[-.37, .36]	-0.37	.582		[-1.69, 0.96]
ΔTOI right Anti (%)	0.60	3.17	[-.12, 1.77]	0.55	1.21	[.14, .94]	-0.05	.929	†	[-1.18, 1.08]
ΔTOI left Pro/Anti (%)	0.35	3.87	[-.64, 1.80]	0.48	1.07	[.13, .78]	0.13	.852	†	[-1.21, 1.46]
ΔTOI right Pro/Anti (%)	0.64	3.22	[-.11, 1.83]	1.16	1.34	[.75, 1.62]	0.52	.375	†	[-0.64, 1.68]

Note. *p*-values obtained using parametric test, bolded if non-parametric test not needed; * = parametric test $p < .05$; † = non-parametric test $p < .05$

Figure 1: During engagement in the visuomotor tasks, anterior frontal oxygenated hemoglobin (Δoxy-Hb in micromoles per liter, μM/l) decreased in young adults but increased in older adults. The Δoxy-Hb increases in older adults amplified with cognitive demands across the tasks, as did performance deficits, providing evidence that the hemodynamic differences were compensatory in nature. Note that reaction time increases in older compared to young adults are listed above the Δoxy-Hb indicators, Δoxy-Hb data are collapsed across the hemispheres as no asymmetries arose, and a Δoxy-Hb value of zero indicates no change from resting baseline. Image created using MRIcron software by Chris Rorden (http://www.nitrc.org/projects/mricron).

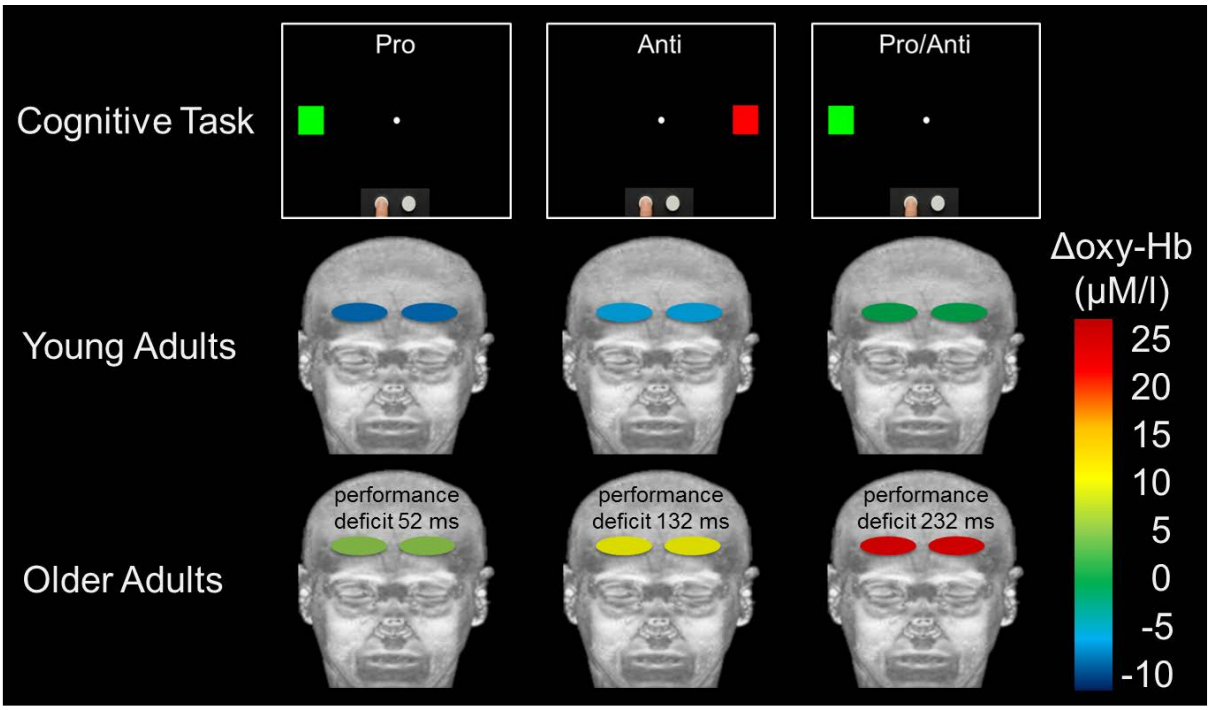

Figure 2. Summary of the changes in oxy-Hb, deoxy-Hb, and total-Hb elicited by engagement in each visuomotor task (Pro, Anti, and Pro/Anti) in young and older adults. Compared to resting baseline, oxy-Hb and total-Hb decreased in young adults but increased in older adults, especially as cognitive difficulty increased across the tasks. The hemodynamic patterns exhibited in older adults indicate relatively greater involvement of anterior frontal cortex as task difficulty increased. Error bars reflect SDs. Significance symbols on bars indicate a difference from resting baseline and across bars indicate a difference between cognitive conditions. † $p < .06$. * $p < .05$. ** $p < .01$. *** $p < .001$.

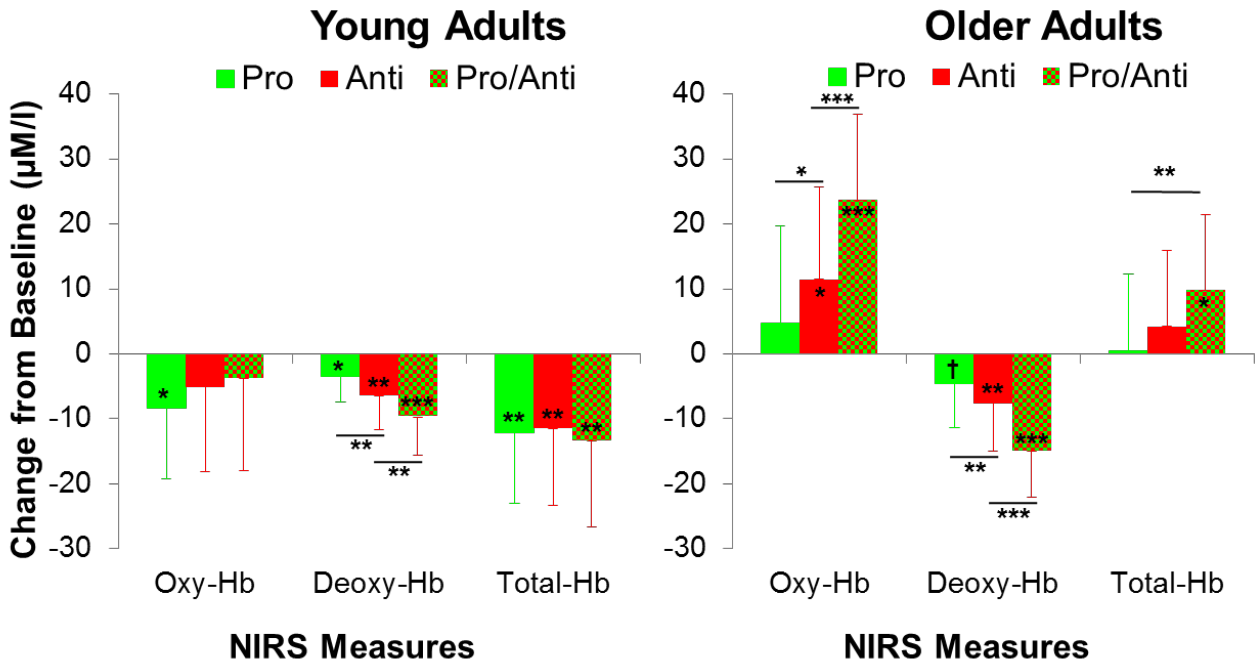

Figure 3. Summary of the changes in tissue oxygenation index (TOI) elicited by engagement in each visuomotor task (Pro, Anti, and Pro/Anti) in young and older adults. Young adults showed no significant changes in TOI, whereas in older adults TOI increased with cognitive task difficulty, indicating increased cerebral blood flow in anterior frontal cortex particularly during the hardest task. Error bars reflect SDs. Significance symbols on bars indicate a difference from resting baseline and across bars indicate a difference between cognitive conditions. † $p = .07$. * $p < .05$. *** $p < .001$.