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Functional near infrared spectroscopy detects cortical activation changes concurrent with memory loss in postmenopausal women with Type II Diabetes

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Abstract

Older adults with Type II Diabetes Mellitus (DM) experience mild cognitive impairment, specifically in the domain of recall/working memory. No consistent causative structural cortical deficits have been identified in persons with DM (PwDM). Memory deficits may be exacerbated in older adult females, who are at the highest risk of cardiovascular decline due to DM. The focus of the current study was to evaluate functional cortical hemodynamic activity during memory tasks in postmenopausal PwDM. Functional Near Infrared Spectroscopy (fNIRS) was used to monitor oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) during memory-based tasks in a cross-sectional sample of postmenopausal women with DM. Twenty-one community-dwelling DM females (age = 65 ± 6 years) and twenty-one age- and sex-matched healthy controls (age = 66 ± 6 years) were evaluated. Working memory performance (via N-back) was evaluated while study participants donned cortical fNIRS. Health state, metabolic data, and menopausal status data were also collected. Deficits in working memory accuracy were found in the DM group as compared to controls. Differences in HbO responses emerged in the DM group. The DM group exhibited

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Code, data, and materials availability Data analyzed in this project will be available via Zenodo (https://zenodo.org/) upon manuscript publication. As public sharing of protected health information such as date of birth, date of diagnosis, dates of treatment and other private medical history information pertinent to each participant may violate HIPAA and the Texas Medical Privacy Act, these data will not be shared to protect patient identity.

Conflict of interest None of the authors has any conflict of interest to disclose.

altered PFC activity magnitudes and increased functional cortical activity across ROIs compared to controls. HbO and HbR responses were not associated with worsened health state measures. These data indicate a shift in cortical activity patterns with memory deficits in postmenopausal PwDM. This DM-specific shift of HbO is a novel finding that is unlikely to be detected by fMRI. This underscores the value of using non-MRI-based neuroimaging techniques to evaluate cortical hemodynamic function to detect early mild cognitive impairment.

Keywords

fNIRS; Cortical oxygenation; Cognition; Brain; Neuroimaging; Dementia

Introduction

Over 14.3 million individuals in the United States aged 60 + are living with either diagnosed or undiagnosed Type II Diabetes Mellitus (DM) (Centers for Disease Control and Prevention 2020). DM and cardiovascular disease are hypothesized to share an underlying constellation of causes, referred to as the 'common soil' hypothesis (Lebovitz 2006). With advanced age, persons with DM (PwDM) exhibit losses in several functional abilities; including development of mild cognitive impairment (MCI), amnesiac mild cognitive impairment (aMCI), and sensorimotor dysfunction (van den Berg et al. 2008; Christman et al. 2009; Janoutová et al. 2015; Gorniak et al. 2019a, b). Patients are not self-aware of these losses (Gorniak et al. 2014) which are typical precursors to development of dementias such as Alzheimer’s disease or vascular dementia.

Emerging evidence reveals differences in presentation of DM and its complications between the sexes with advanced age (Seghieri et al. 2017; Campesi et al. 2017b; Centers for Disease Control and Prevention 2020). Older adult women are significantly more negatively impacted by risks, complications, and comorbidities associated with DM, including development of dementia (Campesi et al. 2017a).

Female participants have been largely excluded from biomedical science for decades, as estrus has been perceived to render females more physiologically variable than males (Beery and Zucker 2011; Prendergast et al. 2014; Vitale et al. 2017). However, sex-based differences in DM presentation and its complications, including cognitive impairment, is an emerging area of interest. Sex-based differences in DM in animal models have not translated well to humans (Campesi et al. 2017b), which has significantly complicated attempts to understand DM-related complications.

Cognitive impairment in memory adversely affects the ability to manage complex daily DM self-management tasks such as meal preparation, taking medications, and exercise (Christman et al. 2009; Vance et al. 2011; Gold 2012). Many of these self-care tasks involve the use of one or both upper extremities in tasks which may require more cognitive resources for successful task completion. Our prior work has found that inclusion of a motor task while performing memory-based cognitive tasks (known as dual-tasking) may lead to reduced accuracy in both cognitive and motor tasks (Gorniak et al. 2019a, b); however, the cortical roots of these deficits are underexplored.

Traditional neuroimaging approaches (i.e., magnetic resonance imaging (MRI)) have been used to search for structural cortical roots of DM-related complications such as MCI and sensorimotor dysfunction (Manschot et al. 2006; Harten et al. 2006; van Harten et al. 2007; Christman et al. 2010; Brundel et al. 2012; Biessels and Reijmer 2014). Inconclusive structural evidence of cortical damage via MRI in individuals with DM has led to investigation of cortical activation differences using functional MRI (fMRI). This is in line with the assumption that altered hemodynamic responses due to micro- and macro-vascular changes are the most likely source of global behavioral changes in individuals with DM (Zochodne 2007). However, inconsistent fMRI evidence of cortical dysfunction in individuals with DM has been reported (Manschot et al. 2006; Harten et al. 2006; van Harten et al. 2007; Christman et al. 2010; Brundel et al. 2012). The blood oxygenation level dependent (known as BOLD) response of fMRI is based on measured changes in one aspect of the hemodynamic response—deoxygenated hemoglobin (HbR) (Buxton 2013). fMRI is only sensitive to HbR (due to its strong paramagnetization (Huettel et al. 2014)), whereas the oxygenated hemoglobin (HbO) aspect of the hemodynamic response is diamagnetic and undetected by fMRI approaches. Acknowledging this shortcoming of fMRI, alternative functional cortical investigations using technologies such as functional near infrared spectroscopy (fNIRS) has revealed altered HbO concurrent with sensorimotor dysfunction in postmenopausal women with DM (Gorniak et al. 2020).

Our overarching hypothesis is that altered hemodynamic function of the cortex leads to DM-complications including cognitive and sensorimotor impairments. In particular, postmenopausal women likely experience significant deterioration of both hemodynamic function and overt behaviors (e.g., cognitive function) given their disproportionate risk of cardiovascular complications as compared to men with DM and individuals without DM (Kautzky-Willer et al. 2016; Raparelli et al. 2017). The focus of this study was to evaluate changes in cortical oxygenation indices of postmenopausal women both with and without DM during memory-based cognitive single- and dual-tasks via fNIRS.

In line with our previous work (Gorniak et al. 2019a, b), we expected to see between-group differences in cognitive function, with impaired memory/recall in the DM group (Hypothesis #1). Concurrent with impaired cognitive function, we expected between-group differences in cortical oxygenation indices of oxygenated hemoglobin (HbO) and deoxygenated/reduced hemoglobin (HbR) (Hypothesis #2) across regions of the cortex involving memory and sensorimotor function during tasks involving cognitive components. No specific hypotheses regarding changes in cortical hemodynamic function with disease state were developed a priori, as multiple mechanistic pathways have been suggested with different levels of support in the evidence base (e.g., high A_{1c}, hypertension, etc.). To examine our two hypotheses, cortical hemodynamic activity was measured via fNIRS during performance of cognitive tasks. The goal of the study was to evaluate the relationship between cortical hemodynamic activity and cognitive function in persons with DM versus controls.

Materials and methods

Participants

Twenty-one postmenopausal women with DM and twenty-one age- and sex-matched healthy controls volunteered to participate in this case control study, see Table 1 for demographics. Handedness was assessed by the Edinburgh Inventory (Oldfield 1971), ranging from a laterality quotient (LQ) of −100 (strong left-handedness) to +100 (strong right-handedness). Participants had an LQ average of +88 and had no previous history of trauma to the upper limbs. Both the DM and control groups included women from self-identified underrepresented racial and ethnic minority groups (n = 24/42 (57%)). Study participants were excluded if they reported a history of neurological and/or musculoskeletal disorders (Parkinson disease, Huntington's disease, polio, multiple sclerosis, stroke, traumatic brain injury, carpal tunnel syndrome, rheumatoid arthritis, Monoclonal Gammopathy of Undetermined Significance (MGUS), Paraproteinaemic Demyelinating Neuropathy (PDN), Myasthenia Gravis), a history of amputation, a history of major surgical intervention to the upper extremity, or hereditary or compression neuropathies. In accordance with the Declaration of Helsinki, participants provided informed consent according to the regulations established by the Institutional Review Board at the University of Houston (protocol #15615–01). Data collection processes failed on five participants (e.g., a reliable fNIRS signal was not detected (control participants #2, #7, and #10; DM participants #9 and #19)). Data from those participants have been excluded from fNIRS analyses but not behavioral data for completeness of reporting.

Health status data

Blood pressure, cholesterol, and glycated hemoglobin (A_{1c}) values were assessed for all study participants onsite at the onset of each session. Cholesterol and A_{1c} values were assessed using a commercially available point of care evaluation kit (Cardiocheck + and A_{1c} Now + kits, PTS Diagnostics, Indianapolis, IN, USA). Blood pressure was measured using a commercially available device (Omron Intellisense 10 series Blood Pressure Monitor, Model BP785, Bannockburn, IL, USA). The presence of peripheral neuropathy (PN status) was determined by abnormalities on either clinical examination or EMG/NCV testing (per physician). A brief menopause questionnaire was also administered regarding several aspects of menopausal characteristics (e.g., age at onset of menopause, hormone replacement therapy history, etc.). All study participants declared themselves to be postmenopausal; with 11 participants claiming a history of hormone replacement therapy (5 with a history of Prempro use). Of the 11 participants with a history of hormone replacement therapy, 4 were in the control group and 7 were in the DM group.

Baseline cognitive evaluation

Montreal cognitive assessment (MoCA)—Cognitive function of each participant was screened using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al. 2005). This is a brief examination of the cognitive domains: attention and concentration, executive functions, working memory/recall, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. The number of years of patient education is

accounted for within the MoCA scoring structure. This evaluation was performed prior to placement of the fNIRS cap.

Experimental tasks

Working memory (N-back) evaluation (single-task)—Working memory of each participant was probed using the working memory (N-back) evaluation while wearing the fNIRS device. Working memory was assessed while participants were seated in a quiet location. This test required participants to repeat the "Nth" word back in a list of random words presented as auditory stimuli, consistent with our prior work (Gorniak et al. 2019a, b). The difficulty level is controlled by requiring participants to remember words further back in the series. Three conditions of the N-back task were assigned to each subject (easiest to most difficult: 0-, 1-, and 2-back conditions) in a block randomized manner. Participants wore a headset with headphone and microphone capabilities (Plantronics Inc., Santa Cruz, California), through which they heard a randomized sequence of words via audio provided by E-prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA). The software program generated randomized words through the headphones at an interval of 2 s per word. Participants were instructed to verbally repeat the words into the headset in the correct sequence for a task duration of 30 s. The rate of correct responses and verbal reaction time were recorded by the E-prime software and extracted to evaluate performance. Three trials were collected in each of the N-back conditions. N-back conditions were block randomized across all participants.

Working memory (N-back) + motor task evaluation (dual-task)

Working memory function was probed at a baseline (single-task) as well as during motor function evaluations (dual-task). All single-tasks occurred prior to dual-tasks to avoid subject confusion. Each subject was asked to perform a series of working memory + motor task (dual-task) interleaved by 30 s periods of rest, see Fig. 1 for details. Presentation of visual stimuli, timing, and synchronization TTL signals were controlled via E-prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA). Three trials were collected in each of the N-back conditions for dual-task evaluation. N-back conditions were block randomized across all participants in dual-task conditions.

During the working memory + motor task, participants used a precision pinch grip to exert an isometric force against a set of force transducers. Participants were instructed to match their pinch force to the target force line as accurately as possible. Two different force levels were tested for the dominant (right) hand (15% MVC and 40% MVC). Three trials of 30 s each, were performed with at 30 s of rest/washout periods between each block. Force level order (15% or 40% MVC) was block randomized.

The motor task involved using digits 1 and 2 in a precision pinch grip to produce a constant level of pinch force, with feedback from a computer screen. All forces and moments of force produced were recorded simultaneously using 2 identical 6-component force-moment transducers (Nano-25 transducers; ATI Industrial Automation, Garner, NC, USA). Instrument details have been published previously (Gorniak et al. 2014; Ochoa and Gorniak 2014).

Cortical hemodynamics measurements

Cortical hemodynamics were measured with a continuous-wave functional near infrared spectroscopy instrument (NIRScout, NIRx Technologies, Glen Head, NY, USA) via 16 optical emitters and 16 optical detectors. Each emitter consisted in a dual-wavelength LED (central wavelengths: 760 nm and 850 nm) directly coupled to the scalp, while each detector was a silicon photodiode collecting backscattered light from the scalp via an optical fiber. The geometrical layout of optical emitters and detectors (collectively referred to as optodes) is shown in Fig. 2A, alongside the corresponding sensitivity map of the optical probing on the cerebral cortex (Fig. 2B) estimated with Monte Carlo-based simulation of photon migration in AtlasViewer (Aasted et al. 2015). We ensured reproducibility of placement to the best of our ability by fitting the standard 10–10 headset (EasyCap, Germany) with reference to anatomical landmarks (nasion Nz, inion Iz, vertex Cz, and preauricular points LPA and RPA), to achieve an optode landing according to the layout depicted in Fig. 2A. We also digitized the spatial location of all optodes and registered such position to a scalp-brain atlas (Colin 27) to ensure placement accuracy within reasonable range (10 mm from standard EEG labels). Regarding the association between optode placements and cortical regions, we inferred cortical areas interrogated by each group of optical channels (ROIs) from the sensitivity map projected onto a Colin 27 model computed with photon migration simulations using AtlasViewer. Although Fig. 2B shows the sensitivity map of the entire probe, we displayed the projections of each ROIs separately and denoted cortical regions accordingly. This configuration resulted in 28 optical channels (i.e., emitter-detector pairings) that interrogated the prefrontal, motor, and somatosensory cortices bilaterally. The geometrical distance between optode pairings ranged from 26 to 37 mm, ensuring the interrogation of the cerebral cortex in all optical channels (Strangman et al. 2013). Proper scalp-optode coupling was ensured by using the PHOEBE toolbox (Pollonini et al. 2016).

Raw optical signals were collected continuously throughout the N-back portions of the experiment at the frequency of 3.91 Hz from all channels at both wavelengths, and were subsequently converted to optical density (i.e., logarithm of the raw intensity) and then to concentration changes of oxygenated (HbO) and deoxygenated hemoglobin (HbR) compared to a zeroed baseline according to the modified Beer-Lambert Law (Cope and Delpy 1988; Delpy et al. 1988). For each channel, HbO and HbR measurements were analyzed separately with a general linear model approach that estimated the scalar weight coefficient (a.k.a., beta weight (Barker et al. 2013)) of the canonical hemodynamic response that best fitted the measured hemodynamic response. The general linear model approach is described in detail in (Santosa et al. 2018). We did not apply particular preprocessing steps to fNIRS data, since autoregressive pre-whitening approach using iteratively reweighted least-squares (AR-IRLS) can deal with data outliers produced by motion artifacts and extracerebral and physiological responses (Santosa et al. 2018). For each subject, we considered channels as hemodynamically active if their weight coefficient was statistically different from zero at the significance level of 5%.

At the group level, we used a mixed linear model to estimate the weighting coefficient of all channels to determine which of them were hemodynamically active at a statistically significant level. We considered the interaction between the experimental condition (N-back

condition) and the group (DM vs. control) as the fixed effect contributing to the weight coefficient, while the magnitude of the coefficient of individual subjects were considered as a random effect.

We grouped optical channels into ten bilateral (right and left) regions of interest (ROIs), namely the prefrontal cortex (PFC), supplementary motor area (SMA), primary motor cortex (M1), primary sensory cortex (S1), and Brodmann Area 40 (B40) as depicted in Fig. 2A. We computed individual-level ROI-level statistics (weight coefficient, *t*-value, *p*-value). Positive HbO values and negative HbR values each indicate cortical activity, respectively. Some ROIs did not produce significant t-scores in HbO or HbR. Those data are shown as zeroes in mean and standard error (SE) values in figures within the results section.

Statistical analysis

The data are presented as means ± SE. For HbO and HbR, statistically significant individual-level ROI *t*-scores were compared between *Groups* using mixed model analyses of covariance (ANCOVAs) via SPSS 25 (IBM Corporation, Armonk, NY, USA). Between-subject primary factors were *Group* (two levels: DM vs. controls). Within-subject factors included *Hemisphere* (two levels for the cortex: left and right) and *ROI* (five levels: 1 = PFC, 2 = SMA, 3 = M1, 4 = S1, and 5 = B40). For N-back data, main factors included: *Group, Task Type* (two levels: one level each for single- and dual-tasks), and *Condition* (three levels: 0-back, 1-back, and 2-back). Evaluation of health state covariates was done to control for health state variability both within and across the two sample groups. Covariates were selected via Automatic Linear Modeling (ALM) using forward stepwise selection functions in SPSS. ALM was utilized to reduce the potential for expectation biases that may occur when hand-selecting potential statistical models. In the event of significant covariates determined via ALM and ANCOVA, follow-up correlation analyses were performed between the health state or performance covariate and the measured behavior. ANCOVAs included health state covariates of: A_{1c}, systolic and diastolic blood pressures, total cholesterol, high-density lipoprotein (HDL) cholesterol, disease duration, menopausal age, body mass index (BMI), PN status (via indicator variable), history of hormone replacement therapy (via indicator variable), history of treatment with Prempro (conjugated estrogens/medroxyprogesterone acetate; via indicator variable), and working memory performance variables of response time and accuracy (in HbO and HbR analyses). Specific attention to use of Prempro in our work is warranted as long-term use of Prempro is associated with development of cardiovascular disease and potential cognitive complications (Wells and Herrington 1999; Grady et al. 2002; Cagnacci and Venier 2019; Manson et al. 2020). Prempro use was largely abandoned in the early 2000's; however, patients with a history of Prempro use are still alive. In multiple comparison situations, Bonferroni corrected posthocs were used. Significant differences are denoted by the following in figures: * at $p < 0.05$, ** at $p < 0.001$, *** at $p < 0.005$, and **** at $p < 0.001$.

Results

Cognitive evaluation

Montreal cognitive assessment (MoCA)—Via ALM, the MoCA data show a significant *Group* difference ($F_{1,42} = 6.45$, $p < 0.05$) in which the average total MoCA scores were lower in the DM group as compared to controls, Fig. 3A. Further analyses of the individual MoCA domains indicated *Group* differences in working memory/recall ($F_{1,19} = 7.27$, $p < 0.05$), such that working memory/recall scores in the DM group were lower as compared to controls. MoCA data scores can be found in Fig. 3B.

Working memory (N-back) evaluations: accuracy

Differences between single- and dual-task accuracy rates were not found via ALM; subsequent analyses of N-back data were performed collapsed across both single- and dual-task conditions. Significant *Group* differences in N-back accuracy were found ($F_{1, 230} = 46.73$, $p < 0.001$); such that the DM group was less accurate than controls (Fig. 3C). *Condition* ($F_{2, 230} = 142.61$, $p < 0.001$) and *Group x Condition* ($F_{2, 230} = 6.29$, $p < 0.005$) effects were found such that accuracy declined as the *Condition* became more difficult; however, the decline in accuracy was more dramatic in the DM group (Fig. 3C). When health state covariates were included in statistical analyses, the *Condition* ($F_{2,123} = 170.39$, $p < 0.001$) effect remained significant. However, health state covariates of *Total Cholesterol* ($F_{1,123} = 9.95$, $p < 0.005$), *Menopausal Age* ($F_{1,123} = 14.47$, $p < 0.001$), and *Prempro Use* ($F_{1,123} = 13.86$, $p < 0.001$) replaced the *Group* effect. These health state covariates were positively correlated with accuracy (*Total Cholesterol:* $r_{264} = 0.277$, $p < 0.001$; *Menopausal Age:* $r_{252} = 0.219$, $p < 0.001$; *Prempro Use:* $r_{252} = 0.137$, $p < 0.05$).

Working memory (N-back) evaluations: response time

Differences between single- and dual-task response times were not found via ALM; subsequent analyses of N-back data were performed collapsed across both single- and dual-task conditions. *Group* differences in N-back response times were found ($F_{1, 217} = 21.20$, $p < 0.001$); such that the DM group had longer response times than controls (Fig. 3D). Significant *Condition* ($F_{2, 217} = 4.72$, $p < 0.05$) and *Group x Condition* ($F_{2, 217} = 3.44$, $p < 0.05$) effects were found such that response times were generally flat in the control *Group* but were significantly higher in the 1-back condition for DM group as compared to all other *Conditions* (Fig. 3D). When health state covariates were included in statistical analyses, the main effects of *Group* and *Condition* disappeared. Instead, *Total Cholesterol* ($F_{1,90} = 16.92$, $p < 0.001$) dominated the model and was negatively correlated with response time ($r_{240} = -0.257$, $p < 0.001$).

Cortical hemodynamic responses

Cortical hemodynamic responses during working memory (N-back) evaluation —ALM analyses indicated significant differences in *Task* in the HbO data, but not the HbR data. In the following paragraphs, we present the HbO data first with results presented in the single-task separate from the dual-task. Afterwards, we present the HbR data collapsed across *Task*, as *Task* was not found to be a significant factor for HbR.

HbO data, single-task

During the single-task working memory evaluation, significant effects of *Group* ($F_{1,76}$ = 4.07, $p < 0.05$), *ROI* ($F_{4,76}$ = 5.40, $p < 0.001$), and *Condition* ($F_{2,76}$ = 5.77, $p < 0.001$) were found in HbO *t*-scores via ALM. Overall, the data show significantly larger average HbO *t*-scores in the DM *Group* as compared to controls; this is particularly noticeable in PFC (between *Group differences* are denoted in Fig. 4A). As the N-back *Condition* became more difficult (0-back vs. 2-back), HbO *t*-scores decreased significantly on average across *ROIs* except for PFC and SMA, denoted in Fig. 5. HbO *t*-scores in PFC were significantly different from S1 and M1 as N-back *Condition* difficulty increased (shown in Fig. 5), supported by a near significant interaction in *Condition x ROI* ($F_{8,76}$ = 1.77, p = 0.096). No health state covariates were found impact to HbO *t*-scores in the single-task condition.

HbO data, dual-task

During the dual-task working memory evaluation, a significant interaction effect in HbO of *Group x Side x ROI* ($F_{13,170}$ = 1.971, $p < 0.05$), shown in Fig. 4B, was found when response time and accuracy were included as covariates within the statistical model via ALM. Posthoc analysis of this data show significantly higher HbO *t*-scores by the DM *Group* in the left hemisphere in the dual-task (most notably in B40 as compared to PFC and M1), denoted in Fig. 4B. No other health state covariates were found impact to HbO t-scores in the dual-task condition.

HbR data, collapsed across task

With respect to HbR, a significant effect of *ROI* ($F_{4,187}$ = 2.60, $p < 0.05$) was found along with a significant *Side x ROI* interaction ($F_{4,187}$ = 3.93, $p < 0.005$) via ALM, as indicated in Fig. 6. HbR *t*-scores showed significant asymmetry in the PFC region, as well as significant differences between PFC and M1 activation in both hemispheres (supported by posthoc testing). No health state covariates were found impact HbR t-scores.

Discussion

The purpose of the current study was to evaluate changes in cortical oxygenation indices of postmenopausal women both with and without DM during cognitive tasks. The data support each of our hypotheses. In support of Hypothesis #1, cognitive impairment in memory/recall was observed in postmenopausal women with DM as compared to controls. Impaired memory function appeared as reduced accuracy and did not differ if the task was performed alone or coupled with a simultaneous motor task. In support of Hypothesis #2, HbO values differed between groups during memory/recall tasks; in some ROIs, differences in HbO were magnified in the DM group, suggesting changes in memory activation patterns with increased functional activity of non-PFC regions in PwDM. With respect to our exploratory arm of the study, there is an influence of poor health state and earlier menopausal age on poor memory function; however, no influence of health state was found to impact HbO or HbR. In the following paragraphs, we discuss the results of this study regarding cortical oxygenation, functional neuroimaging, the impact of health state markers, and menopause in assessment of both behavior and cortical hemodynamic function.

DM-changes in hemodynamic response and use of fNIRS

The data indicate a significant difference in the use of HbO concurrent with impaired memory function, such that the DM group exhibited differences in PFC HbO activity during dual-tasks and dedifferentiation of functional brain activity across remaining ROIs as compared to controls. Functional activity changes concurrent with deficits in working memory in the DM group indicate a functional root for memory deficits in persons with DM that is linked to HbO. This is consistent with our recent finding of altered cortical HbO use in PwDM in sensorimotor tasks (Gorniak et al. 2020). Together, these data indicate that it is a problem with the hemodynamic response that leads to behavioral deficits in DM. This supports use of behavioral monitoring along with fNIRS to detect early MCI development since techniques such as fMRI rely on the paramagnetism of HbR, thereby not fully measuring cortical hemodynamic activity which involves both HbO and HbR. Increased HbO use during dual-tasks is notable in the DM group, as HbO use is not indicated by other functional imaging techniques—including fMRI. By its nature, HbO is diamagnetic and not attracted to any magnetic field. Use of (f)MRI also limits the possible sample for study participants, as implanted devices (e.g., stents, pacemakers, etc.) commonly used to treat cardiovascular comorbidities of DM are an exclusion criterion for (f)MRI (Manschot et al. 2006; Harten et al. 2006; van Harten et al. 2007; Christman et al. 2010; Brundel et al. 2012). Techniques such as fNIRS offer better insight into cortical activity using a more inclusive approach that may better reflect early markers of MCI during realistic tasks similar to activities of daily living in populations at high risk of developing dementia (Pinti et al. 2020). Aberrations in cortical activity may be a potential biomarker for tracking changes in cognitive decline in DM using wearable technology such as fNIRS ahead of development of dementias such as Alzheimer’s disease. Detection of cortical activity differences via fNIRS provides an inclusive approach and expands monitoring eligibility for persons with implanted devices (e.g., stents, pacemakers, etc.). This is consistent with other work done in fNIRS supporting its use in investigating cognitive function with respect to both advanced age and disease (Sato et al. 2013; Bonetti et al. 2019; Beishon et al. 2021; Koo et al. 2022; St George et al. 2022; Hou et al. 2002).

Significantly different use of HbO in the cortex in DM may indicate reduced bioavailability of oxygen in DM; consistent with evidence of behavioral impairment in DM (Gorniak et al. 2020). However, the change in HbO use in the DM group during dual-tasks was not accompanied by improved memory, as accuracy and response time were generally worse in the DM group across all conditions. DM is associated with increased hemoglobin-oxygen affinity, which is responsible for lower oxygen delivery rates to tissue (Pu et al. 2012). DM is also associated with impaired hyperemic response, endothelial dysfunction, and microvascular dysfunction (Meyer et al. 2008; Petrofsky 2011; Barwick et al. 2016; Pollonini et al. 2020). However, the increased use of HbO in the DM group within the current data set indicate that increased hemoglobin-oxygen affinity does not contribute to the observed memory deficits; rather the impairment in vascular function drives memory deficits in DM.

Impaired memory function and cortical activity changes in DM

The DM group exhibited significant bilateral PFC activation via HbO in dual-tasks as compared to controls, despite memory error rates not improving with increased PFC activity. These activity differences co-occurred with activation of non-PFC cortical areas involved in movement, priming for movement, phonological processing, and emotional responses (M1, SMA, and B40 respectively). This DM-specific shift in HbO use is a novel finding that cannot be detected by fMRI. An increase of HbO along with higher HbO values in other measured ROIs suggests distributed cortical HbO activity in DM in an attempt to compensate for memory deficits. This change in HbO was not accompanied by *Group* differences in HbR use, suggesting that altered HbO use across the cortex is the driver of memory deficits in DM. Changes in HbO in the DM group are supported by evidence of increased HbO use in the primary visual cortex in PwDM during visual stimulation (Aitchison et al. 2018), and may suggest an increased sympathetic drive in the autonomic nervous system in postmenopausal women (Barnes et al. 2014). These differences may also suggest potential advanced aging of the brain via cortical dedifferentiation in PwDM beyond what is to be expected with healthy aging (Koen et al. 2020; Seider et al. 2021; Rabipour et al. 2021).

Changes in PFC activity in HbO use are consistent with reports of hypothalamic–pituitary–adrenal axis (HPA) dysfunction, insulin signaling aberrations, and pathological changes in hippocampal functions all associated with DM (Sullivan and Gratton 2002; Eichenbaum 2017; Soto et al. 2019). The PFC-hippocampus interaction is known to be important for episodic memory (Eichenbaum 2017). Metabolic disruption of PFC-hippocampus via endocrine dysfunction in DM impacts memory and behavior (Sullivan and Gratton 2002; Ho et al. 2013). Aberrations in PFC activity spurred by changes in the HPA axis in DM are consistent with impaired stress coping ability and symptoms of cognitive decline (Sullivan and Gratton 2002; Ho et al. 2013)—in line with our observations of impaired working memory in DM (Gorniak et al. 2019a, b).

Influence of health state variables and menopause

Reports of the link between metabolic syndrome and cognitive impairment abound in the evidence base (Yaffe et al. 2004). This is supported by our findings of some health state markers (e.g., lipidemia) being associated with impaired memory function in DM (Gorniak et al. 2019a, b), such that PwDM on statins for lipidemia exhibit lower total cholesterol scores but impaired memory function as compared to controls with higher total cholesterol scores who may not take statins for lipidemia management. No significant influences of health state variables on cortical activity were found in the current study. Our prior work on sensorimotor function indicated that health state variables clarified functional cortical activity deficits in DM. The lack of similar result in the current data indicate that hemodynamic response of some cortical regions may not be moderated by commonly measured health state variables (e.g., cholesterol). Cortical regions closely linked to the limbic system, such as PFC and B40, may be more significantly impacted by disruptions to the neuroendocrine system instead. Such disruption may impact cortical activity by blunting both neurovascular and hemodynamic responses (Drew 2019).

Consistent with (Grady et al. 2002), working memory data was impacted by menopausal age and use of specific hormone replacement therapies (HRT). Increased menopausal age (resulting in a shorter time between menopause and participation in the current study) and Prempro use were associated with higher working memory accuracy. Menopausal age was significantly different between the DM (43 ± 11 years) and control (50 ± 7 years) groups (t_{40} = 2.85, $p < 0.05$); however, DM-related deficits in accuracy persisted once menopausal age was considered in our statistical models. In contrast, no significant influences of menopause or HRT were found on cortical activity. The lack of a specific impact of menopausal age on cortical hemodynamic response during memory tasks is an intriguing outcome, as menopause is associated with impaired hemodynamic responses of the cortex and skeletal muscle during sensorimotor tasks (Pollonini et al. 2020; Gorniak et al. 2020). There is some evidence that HRT improves hemodynamic responses in postmenopausal females (Peterson et al. 2000; Fadel et al. 2004); however, it is unclear if HRT is also protective against deficits induced by a combination of DM and menopause. It is also unclear if and how HRT during a certain time window (e.g., early) during menopause may protect both cardiovascular and cognitive function (Grady et al. 2002; Cagnacci and Venier 2019; Manson et al. 2020). A complex interplay among menopause, menopausal symptoms, sex-hormones, and cognitive decline has been suggested (Maki 2015; Cagnacci and Venier 2019; Manson et al. 2020; Maki and Thurston 2020); however, further work is needed to assess what features of menopause may truly underlie memory decline in women, particularly women with DM.

Conclusion

Deficits in working memory accuracy were found in the DM group as compared to controls. Differences in HbO responses occurred such that the DM group exhibited altered PFC activity magnitudes and evidence of increased of functional cortical activity across remaining ROIs. HbO responses in the DM group were not associated with worsened health state measures (e.g., lipidemia). These data indicate a shift in cortical activity regarding memory use in DM concurrent with poor memory. This DM-specific shift of HbO use is a novel finding that cannot be detected by fMRI and is consistent with HPA dysfunction. This work underscores the value of using wearable non-MRI-based neuroimaging technology to monitor functional deficits to detect mild cognitive impairment using a more inclusive approach.

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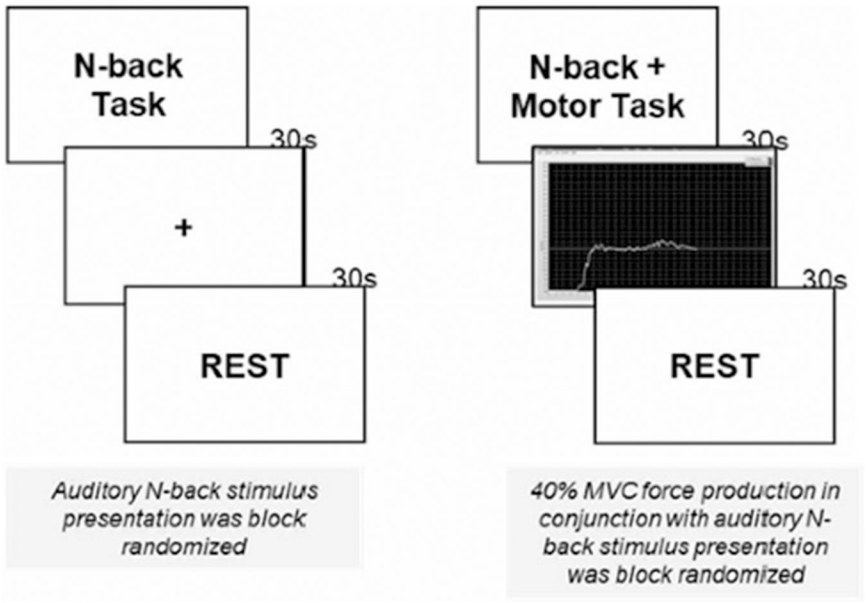

Fig. 1.

Illustration of experimental stimuli during the N-back single task and N-back + motor performance (dual-task) during fNIRS testing. Subjects viewed a fixation cross during N-back single task blocks; they viewed real-time feedback on their force production during N-back + motor performance (dual-task) blocks. The order of N-back presentation was block randomized within each testing type. N-back single task tasks always occurred prior to N-back + motor performance dual-tasks

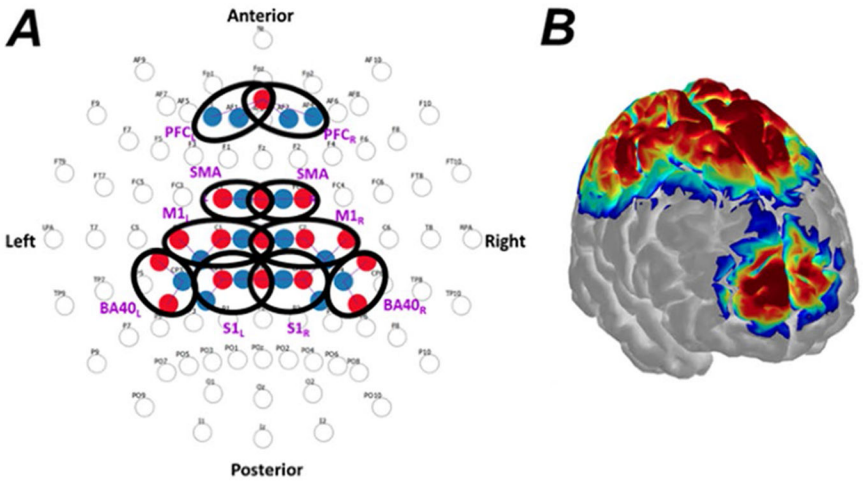

Fig. 2.

Cortical fNIRS layout and sensitivity map. **A** Geometrical layout of sources (red) and detectors (blue) with respect to the international 10–10 EEG system (Oostenveld and Praamstra 2001). Bold black ovals denote the regions of interest (ROIs), which are subsequently labeled nearby in purple boldface. ROIs included: prefrontal cortex (PFC), supplementary motor area (SMA), primary motor cortex (M1), primary sensory cortex (S1), and Broadmann Area 40 (B40). Hemisphere side as well as anterior and posterior of the cranium are noted. **B** Correspondent sensitivity map overlaid onto the Colin27 brain model. Sensitivity computed and displayed with AtlasViewer (Aasted et al. 2015)

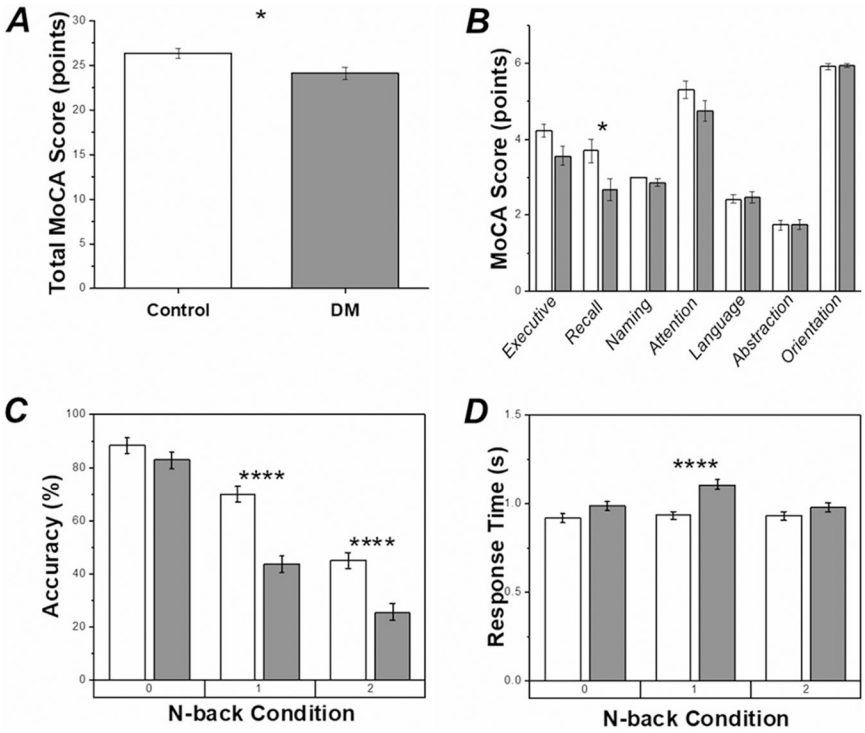

Fig. 3.

Group mean and standard error (SE) for MoCA and working memory data. White bars indicate data from the control group, gray bars indicate data from the DM group. Significant differences between Groups at $p < 0.05$ (*) and $p < 0.001$ (****) are shown. **A** Total MoCA scores. **B** Domain specific MoCA scores. **C** Correct response rates (accuracy) in N-back evaluations. **D** Response times in N-back evaluations

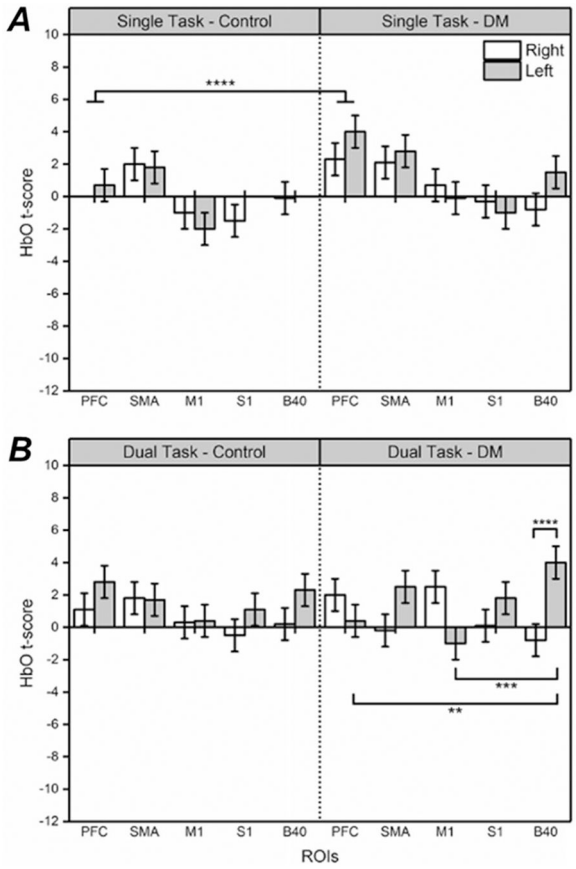

Fig. 4.

fNIRS t-scores for HbO during single-task and dual-task evaluations for each *Group*, depicted by *ROI* and *Hemisphere*. Mean and standard error (SE) values are shown. Significant at $p < 0.01$ (**), $p < 0.005$ (***), $p < 0.001$ (****) are shown. White bars indicate right hemisphere, gray bars indicated left hemisphere

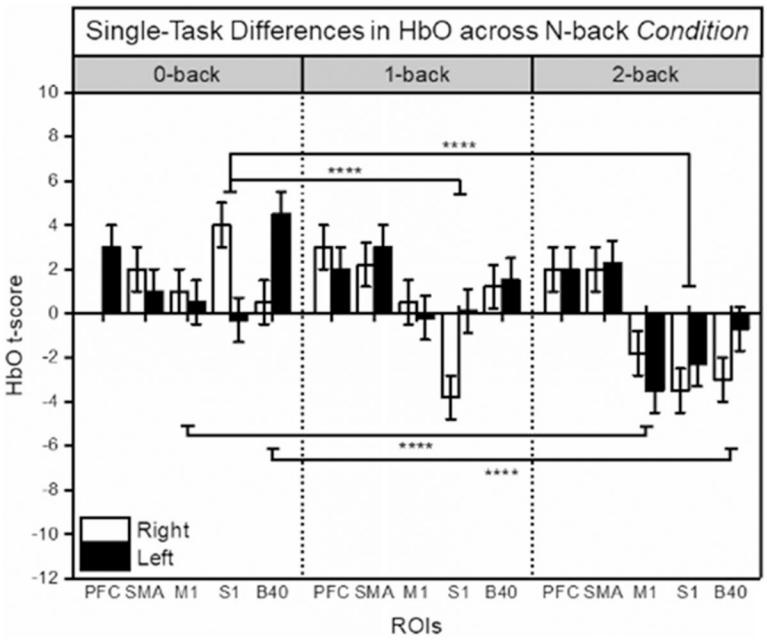

Fig. 5.

fNIRS t-scores for HbO during N-back single-task evaluations (0-, 1-, and 2-back Conditions), depicted by ROI and Hemisphere. Data are averaged across *Group*. Mean and standard error (SE) values are shown. Significant differences between N-back *Conditions* at $p < 0.001$ (****) are shown. White bars indicate right hemisphere, black bars indicate left hemisphere

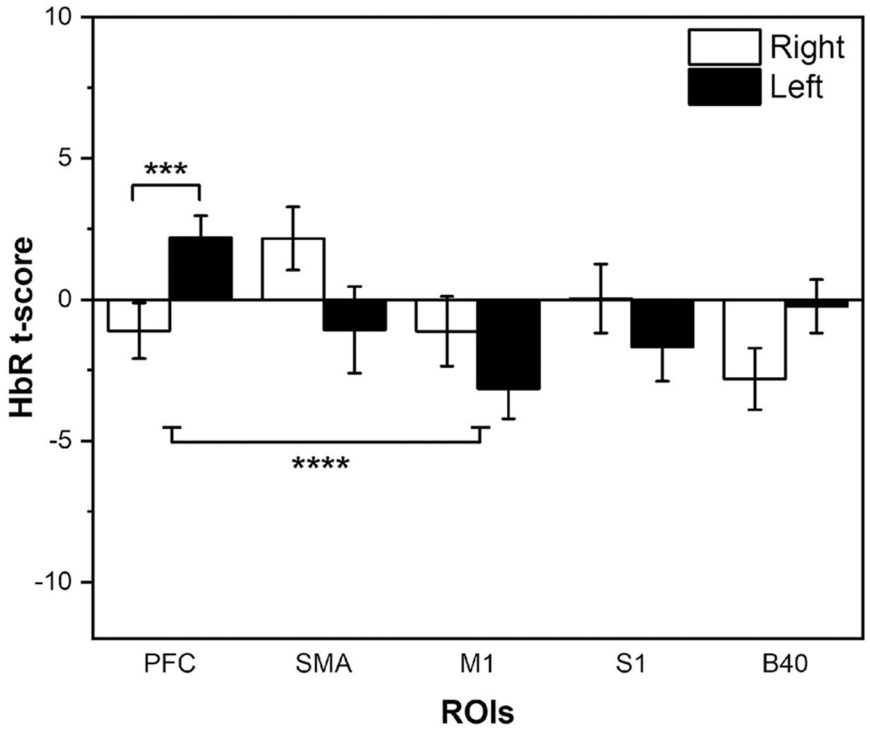

Fig. 6.

fNIRS *t*-scores for HbR collapsed across all Tasks and Conditions, depicted by ROI and Hemisphere. Mean and standard error (SE) values are shown. Significant differences at $p < 0.005$ (***) and $p < 0.001$ (****) are shown. White bars indicate right hemisphere, black bars indicated left hemisphere

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Table 1

Demographic and clinical characteristics of DM participants

Participant #	Age (years)	Menopausal age (years)	BMI (kg/m^2)	DM duration (months)	A_{1c} (%)	Total cholesterol (mg/dL)	Systole (mmHg)	Diastole (mmHg)
1	63	50	27.4	60	6.7	–	151	81
2	79	45	28.3	144	7.9	–	155	75
3*	65	50	40.7	120	7.1	–	145	97
4ǂ	66	50	29.3	186	8.7	199	111	62
5*	64	40	44.1	60	6.2	109	180	91
6	60	50	37.5	387	10.4	224	161	78
7*	60	55	33.7	245	8	143	130	70
8	57	49	36.9	41	8.6	176	130	88
9^	73	60	25.3	201	6.8	125	167	78
10	68	23	31.8	168	5.7	219	164	89
11	70	45	26.9	200	6.1	266	130	71
12	62	38	32.4	36	6.2	189	124	70
13	67	45	30.2	1	8	144	158	97
14*ǂ	66	45	31.4	262	6.3	175	142	75
15*	69	55	42.3	298	8.4	185	139	63
16	58	51	32.8	95	7.4	143	153	89
17*	55	27	38.6	385	7.4	126	133	68
18	67	25	30.5	1	7.7	183	148	73
19*^	71	52	42.9	196	8.5	173	105	60
20	69	27	36.3	149	8.7	187	202	100
21	60	37	30.1	1	6.7	183	179	111
Mean	65	43	33.8	154	7.5	175	148	80
SD	6	11	5.6	117	1.2	39	23	14
Controls	67 ± 6	50 ± 7	24.1 ± 4.5	N/A	5.3 ± 0.3	200 ± 43	147 ± 21	86 ± 14

* Indicates a clinical diagnosis of diabetic peripheral neuropathy

‡Indicates a history of Prempro Rx (in addition to 3 control participants); – Indicates lipid data collection failure; *SD* standard deviation

^indicates omitted fNIRS data due to lack of reliable signal