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Patricia Shewokis

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RESEARCH ARTICLE

Assessment of Prefrontal Cortex Activity in Amyotrophic Lateral Sclerosis Patients with Functional Near Infrared Spectroscopy

Hasan Ayaz[1,*], Patricia A. Shewokis[1,2], Lauren Scull[3], David J. Libon[3], Sara Feldman[3], Joel Eppig[3], Banu Onaral[1], and Terry Heiman-Patterson[3]

[1]*School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA 19104, USA*
[2]*Nutrition Sciences Department, College of Nursing and Health Professions, Drexel University, Philadelphia, PA 19102, USA*
[3]*Department of Neurology, College of Medicine, Drexel University, Philadelphia, PA 19102, USA*

Cognitive impairment in amyotrophic lateral sclerosis (ALS) is associated with cortical changes beyond the motor cortex. The overall goal of this project is to determine if task induced hemodynamic changes detected by functional near infrared (fNIR) spectroscopy from the anterior prefrontal cortex (PFC) has discriminant validity across ALS ($n = 17$) patients and matching healthy ($n = 17$) controls. The experimental protocol was composed of the King-Devick Test, the Number Interference Test and a Continuous Performance Test targeting a range of cognitive domains including sustained attention and executive function. Results indicate that fNIR measures provided significant differences between ALS and healthy controls in all three tasks providing an additional metric for the assessment of cognitive decline. Although this is a pilot study, given the safe, wearable and real-world validity of fNIR, these results may set the foundation for the use of fNIR as a clinical tool in monitoring progression of neurocognitive decline in a simple, less invasive and objective manner than allowed by current imaging technology.

KEYWORDS: Functional Near Infrared Spectroscopy, Amyotrophic Lateral Sclerosis, Prefrontal Cortex, Sustained Attention, Executive Function, fNIR, NIRS, ALS, Optical Brain Imaging.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease, is characterized pathologically by progressive loss of upper motor neurons in layer 5 of the cortex and lower motor neurons in brainstem motor nuclei and anterior horn of the spinal cord. ALS generally presents with progressive weakness, muscular wasting, and spasticity, starting segmentally either bulbar or single limb regions before becoming widespread and producing death from respiratory failure at 2–3 years post-diagnosis for bulbar onset cases and 3–5 years post-diagnosis for limb onset cases [1]. While cognition is assumed to be intact, thereby ensuring competence at decision making, recent evidence suggests deficits in frontally-mediated executive skills occur in a sizable group of ALS patients [2–5]. Cognitive deficits in ALS can range from mild impairment to severe frontotemporal lobar dementia (FTD) [2] and has been detected in up to 50% of patients. The impact that this cognitive involvement may have on the clinical care and decision making through the course of the illness cannot be overestimated. First, the issue of cognitive impairment will influence routine management. For example, dementia patients often need simpler tools for communication and more involvement of the caretaker. Nutritional maintenance may require closer supervision and the presence of cognitive impairment also affects a patient's ability to ambulate safely, given the loss of impulse control. Furthermore, mental competency will have to be carefully scrutinized because ALS patients and their families often face decisions regarding a patient's disability and autonomy.

The study of neurocognition in ALS is an evolving field. Although pathologic and genetic evidence shows an overlap between ALS and FTD, cognitive and behavioral syndromes also occur among patients who have ALS, which cannot be characterized with actual FTD. In fact, evidence of impairment can be detected in up to 50% of patients on the basis of neuropsychological testing, and it has been estimated that FTD occurs in 5–41% of patients [6–8]. The

*Author to whom correspondence should be addressed.
Email: hasan.ayaz@drexel.edu
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terms *ALSci* (ALS with neurocognitive impairment), *ALSbi* (ALS with behavioral impairment), and *ALS-FTD* has been suggested to identify different phenotypes within ALS [4].

Neurocognitive impairment in ALS patients (ALS*ci*) has an estimated prevalence from 10–75% [6, 9]. Most ALS patients with cognitive impairment present with frontally-mediated dysexecutive impairment [7, 10–14] and primarily affected cognitive functions include attention [15], cognitive flexibility [15, 16] and executive function [10, 11, 14, 17]. There may also be an increased association of ALS*ci* with bulbar involvement, dysarthria or pseudobulbar affect [11, 14, 18, 19].

Recent research suggests that abnormalities of cognition are due to pathologic changes outside the motor cortex and are located in the frontal and temporal cortex. For example, impaired verbal fluency, both letter and category fluency, has been reported in a number of studies implicating deficiencies in frontal or striatofrontal areas that are involved in response initiation [6, 7, 15]. Also, decreased working memory capacity, sustained attention and response inhibition has been identified in behavioral and neuroimaging studies, again implicating prefrontal areas [20, 21]. For instance, in a recent study, the authors used an extensive protocol of neuropsychological tests together with event related potential (ERP) recordings [21]. Their results indicated significant performance impairments in cognition including working memory and sustained attention; and these authors concluded a dysfunction of frontal network from the concurrent ERP recordings. Functional magnetic resonance imaging (fMRI) has been used to identify abnormal brain function in ALS patients during cognitive task performance [22, 23] and task-less resting-state analysis [24]. Many other studies, such as cortical metabolism [6, 25–27], pathologic examination of frontal and prefrontal lobe white matter [28–30], voxel-based morphometry [31] and positron emission tomography (PET) [19, 32] implicated frontal areas. A recent comprehensive review has been reported by Goldstein and Abrahams [5] and the authors emphasize that the standard assessment procedures are not appropriate to assess the cognitive status of patients and that new screening tools and technologies with real world validity are needed [5].

It would be extremely useful to be able to detect pathophysiologic changes in the frontal lobe that correlate with cognitive involvement in ALS patients. In fact, there has been significant progress made over the last decade in understanding the neural bases of cognitive processes and behavior. Traditional neuroimaging tools such as fMRI can provide high spatial resolution of neural hemodynamic changes noninvasively. However, data collection procedures (i.e., requirement of patients to stay in a confined space and in a supine position, noisy operation, sensitivity to motion artifact and an expensive setup) limit the widespread use for data collection in outpatient settings. The introduction of new portable and wearable brain imaging tools, that allow monitoring brain activity in ecologically valid environments, would allow for better identification of neurophysiological markers that can index impending cognitive dysfunction and are better suited for continuous monitoring to assess longitudinal changes.

Functional near infrared spectoscopy (fNIR) is a promising brain imaging technology that relies on optical techniques to detect changes in the hemodynamic response within the cortex in response to sensory, motor, or cognitive activation settings [33–38] and on subject populations from newborns to elderly [39–42]. Optical brain imaging is utilizing near infrared light and is based on absorption characteristics of hemoglobin which has a distinct spectra as oxygenated hemoglobin (oxy-Hb) and deoxygenated-hemoglobin (deoxy-Hb) [34, 42–46]. Using multi-wavelength spectroscopy, regional concentration changes in these molecules can be tracked within the cortical tissue [41, 44]. fNIR is safe, non-invasive, affordable, and highly portable, and offers good spatial resolution. Given its characteristics, fNIR alleviates many of the limitations of the traditional neuroimaging techniques by potentially allowing for unrestricted and convenient imaging of brain activity even online as data is collected and also with wireless and battery-operated instruments that are now available [47]. This makes fNIR suitable for the study of neurocognition in the clinician's office or in the home during performance of everyday activities.

The overall goal of this study was to determine if prefrontal hemodynamic changes detected by fNIR during neurocognitive testing differ in ALS subjects when compared to healthy controls. Preliminary studies showed that fNIR can be used to assess cognitive task induced changes in healthy participants [38, 48–52] and ALS patients [53, 54]. The resultant metabolic correlates of neural activation during task performance could provide a highly complementary measure of function in conjunction with neuropsychological testing.

METHODS

Participants

Thirty-four participants ($n = 17$, male) took part in this study, 17 ALS patients (Age = Mean + SD; 57.3 ± 7.5 yrs) and 17 healthy control (HC) subjects (Mean Age = 55.1 ± 6.3 yrs) participated. Prior to the study, all participants were consented and written informed consent was obtained based on the approved protocol by the Institutional Review Board of Drexel University College of Medicine and consistent with the Declaration of Helsinki. The ALS functional rating scale-revised (ALSFRS-R) [55] and Philadelphia Brief Assessment of Cognition (PBAC) [56] were used to assess motor and cognitive performance (See Table I) of the ALS patients.

Experiment Protocol

The experimental protocol was composed of three tests: the Number Interference Test (NIT), King-Devick Test

Table I. ALS functional rating scale-revised (ALSFRS-R) and Philadelphia brief assessment of cognition (PBAC) scores for participants.

Patient									Controls			
				ALSFRS-R								
#	Age	Gender	PBAC	Bulbar	Upper	Lower	Respiratory	Total	#	Age	Gender	PBAC
1	66	M	84.50	11	8	6	11	36	18	64	F	74.00
2	59	M	79.50	12	8	11	12	43	19	54	F	81.00
3	58	M	73.50	9	8	6	4	27	20	42	F	80.50
4	50	M	82.00	12	11	9	11	43	21	49	M	82.00
5	59	M	86.50	9	8	5	10	32	22	58	F	85.50
6	57	M	81.00	12	4	9	12	37	23	56	F	81.00
7	64	F	81.50	12	10	6	12	40	24	65	M	89.00
8	51	M	81.00	7	10	12	12	41	25	53	F	77.50
9	47	M	83.50	12	8	7	11	38	26	55	F	85.50
10	60	F	82.50	12	8	7	11	38	27	55	M	77.50
11	66	F	73.00	8	5	5	5	23	28	58	F	84.00
12	61	M	78.00	10	3	7	12	32	29	54	M	79.50
13	43	M	75.50	7	7	5	4	23	30	46	F	79.00
14	65	F	78.00	4	10	8	5	27	31	47	M	77.00
15	63	F	72.50	11	10	5	12	38	32	60	F	81.50
16	44	F	79.00	12	8	6	12	38	33	58	F	70.00
17	61	M	61.50	6	12	11	11	40	34	62	M	81.50
Mean	57.29		78.41	9.76	8.12	7.35	9.82	35.06		55.06		80.35
SD	7.54		5.95	2.56	2.39	2.29	3.11	6.56		6.32		4.51

(KDT), and a continuous performance test (CPT). All tests were completed within a single 60 minute session.

The NIT is a computerized task modeled after the Stroop Color-Word Interference Test [57]. This test is composed of three test conditions and in each condition period the participants are required to complete 60 single digit addition and multiplication problems by entering the answers on a number pad. During the first trial, subjects were asked to add (e.g., $5+4$) or multiply (e.g., 3×6). In the second trial, the task become more challanging as participants are asked to carry out opposite operations for all problems, that is "+" for multiplication and "×" for addition. In the last condition, requested arithmetic operations were represented by objects with different shape and color (e.g., a green square indicates addition).

The KDT test [58, 59] assesses speed for rapid number naming (reading aloud single-digit numbers from 3 test cards) and captures impairment of eye movements, attention, language, and other correlates of suboptimal brain function [58]. In this study one practice card and 3 test cards were used that contained an irregular matrix of numbers that are identical to stimuli used by Galetta et al. (2011). Standardized instructions were used, and the test required less than 2–3 minutes to administer. During the test participants were asked to read the numbers on each card, line by line and from left to right as quickly as possible but without making any errors. Numbers of errors (and type) made in reading the test cards were recorded. Types of error include skipping numbers, or lines and incorrectly reading numbers.

The CPT is a sustained-attention, reaction-time task that measures the speed with which subjects respond to a stimulus [60]. The CPT is a simple task where the subject presses a button as soon as a target appears on the computer screen. In this study, we used a modified reaction-time/attention task developed in our lab with a duration of 5 minutes and required participants to have continuous performance throughout the task period. During the task, a series of single-digit numbers (between 1 and 9) appeared on the screen at a rate of a digit per second. Subjects were asked to press a trigger hardware button as fast as possible only when the number presented was in the color red. The total number of stimuli presented was 300 with 45 targets arranged in a pseudo-random sequence. Both NIT and CPT tasks were implemented in E-prime (Pschology Software Tools Inc.; www.pstnet.com).

Data Acquisition and Processing

During all three tests, the anterior prefrontal cortex of each participant was monitored with the fNIR system that was first described by Chance et al. (1998), further developed at Drexel University (Philadelphia, PA), manufactured and supplied by fNIR Devices LLC (Potomac, MD; www.fnirdevices.com). The system was composed of three modules: a flexible headpiece (sensor pad), which holds light sources and detectors in a fixed integrated pad to enable a fast placement; a control box for hardware management; and a computer that runs the data acquisition [37].

The positioning of the light sources and detectors on the sensor pad yielded a total of 16 active optodes (channels) and was designed to monitor dorsal and inferior frontal cortical areas underlying the forehead (see Fig. 1) [38, 61]. Anatomical landmarks were used to ensure consistency of sensor placement as described in Ayaz et al. (2011). The sensor grid of 16 optodes has a temporal resolution

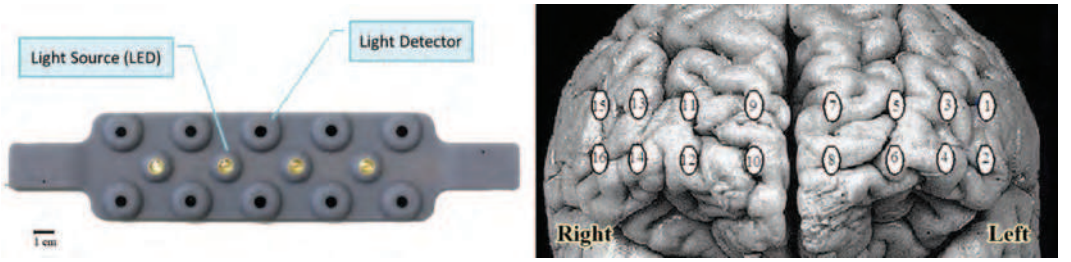

Fig. 1. Flexible fNIR head sensor with 4 LEDs and 10 detectors collect data from 16 measurement locations over forehead (Ayaz et al. 2012).

of 500 milliseconds per scan for each optode. The light emitting diodes (LED) were activated one light source at a time and the four surrounding photodetectors around the active source were sampled. Cognitive optical brain imaging (COBI) studio software (Drexel University) was used for data acquisition and visualization [37].

Details regarding data processing can be found in Ayaz et al. [38]. For each participant, raw fNIR data (16 optodes × 2 wavelengths) were low-pass filtered with a finite impulse response, linear phase filter with order 20 and cut-off frequency of 0.1 Hz to attenuate the high frequency noise, respiration and cardiac cycle effects [36, 37]. Each participant's data was checked for any potential saturation (i.e., when light intensity at the detector was higher than the analog-to-digital converter limit) and motion artifact contamination by means of a coefficient of variation based assessment [62]. fNIR data for each task block were extracted using time synchronization markers received through a serial port during the experiment and hemodynamic changes for each of the 16 optodes during each trial block were calculated separately using the Modified Beer Lambert Law (MBLL). The hemodynamic response at each optode was averaged across time for each trial block to provide a mean hemodynamic response at each optode for each block. The final output of each optode was mean block total hemoglobin (Total Hb) which is the sum of deoxygenated hemoglobin and oxygenated hemoglobin and has been shown to have better spatial specificity compared to other measures in a simultanous fMRI-optical and optical brain imaging studies [63, 64].

Statistical Analysis

Linear mixed effects models (LMM) were calculated on cerebral hemodynamics and behavioral performance using NCSS 9 (Kaysville, UT; www.ncss.com) for estimating fixed and random coefficients. Within the model building, subjects were a random effect while fixed effects included group (ALS and healthy controls-HC). The task condition, for KDT and NIT, included 3 trials and was treated as a repeated measure. The dependent measures included response time and accuracy for the NIT and CPT tasks while average completion time and accuracy were assessed on the KDT.

The application of LMM allows for unequal numbers of observations per participant, does not require normality assumptions typically needed in parametric assessments and can be applied to repeated measures assessments [49, 65]. Model fit was done by restricted maximum likelihood estimates (REML) as well as providing a basis for the relative goodness of fit for a model along with the information criteria. The Akaike Information Criterion corrected for small sample size (AICc) was the information criterion used for model selection [66]. For each measure and model, the model with smaller values of the AICc indicated a better fit and a significance criterion of 0.05 was used. Cohen's d effect size index was used to aid in the interpretation of significant group main effects.

RESULTS

For each task (NIT, KDT and CPT), the behavioral and neuroimaging results are listed in separate subsections below. The following table summarizes the ALSFRS-R and PBAC scores for the patients.

NIT Task

Behavioral Measures

Average response time (RT) to stimulus across all 3 trials for the ALS group was (mean + SD) 3.55 ± 1.1 seconds and for the HC group was (mean + SD) 3.11 ± 1.0 seconds with a $d = 0.59$, whereas the accuracy (correct response) for the ALS group was 0.96 ± 0.04 (over 1.0) and for HC group was 0.96 ± 0.03 (over 1.0). Average RT increased for both groups across trials. This pattern of slower response time is expected when task difficulty proceeds from the sequential lower to higher levels of difficulty from trial 1 through trial 3 in the NIT. As illustrated in Figure 2, there was a significant main trial effect for RT ($F_{2,4} = 138.26$, $p < 0.001$) across the three test trials, but no significant differences across groups. Also, there were no differences in task accuracy across group ($F_{1,33.3} = 0.06$, $p > 0.8$) and trials ($F_{1,45} = 1.61$, $p > 0.2$).

fNIR Measures

There was a significant interaction between group (ALS vs. HC) and task NIT test condition (trials 1, 2, 3) only at optode 12 in HbT ($F_{2,54.5} = 4.07$, $p < 0.05$). The effect sizes for comparison of ALS versus HC across the three test trials were $d = 1.27$, 0.54 and -0.23 for trials 1, 2 and 3, respectively. Positive d values indicate a higher score or activation level for the ALS group. There were

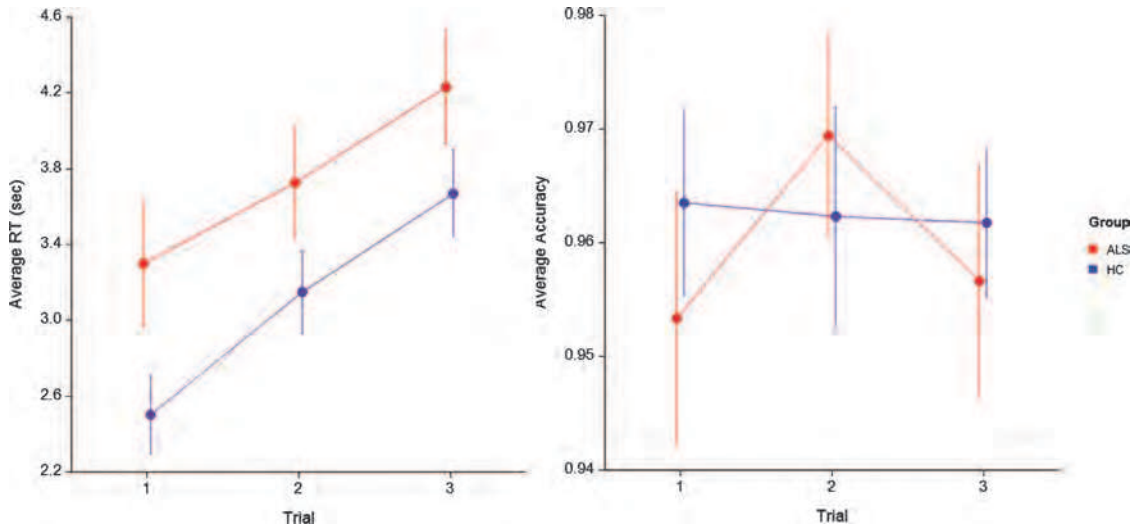

Fig. 2. Average response time (left) and accuracy (right) for NIT task across the groups. Error bars are standard error of the mean (SEM).

no significant main effects detected. Depicted in Figure 3, opposite trends occurred in ALS (red) and HC (blue) groups. As the difficulty in NIT task conditions increased, there was a concomitant increase in activation level in the healthy controls. In contrast, the activation level was highest at the beginning for the ALS group and it decreased with subsequent trials.

KDT Task

Behavioral Measures

Average task completion time was (mean $\pm$ SD) 25.04 ± 8.01 seconds and 19.88 ± 4.17 seconds for the ALS and HC groups, respectively. There was a significant main effect of group (ALS vs. HC) in task completion time of KDT ($F_{1,32} = 6.765$, $p < 0.05$, $d = 1.20$) (see Fig. 4). There were no differences across trials.

fNIR Measures

There was a significant main effect for group on optode 1 (left, lateral) and optode 7 (medial) ($F_{1,15.6} = 4.955$, $p < 0.05$, $d = 0.80$ and $F_{1,31.5} = 4.176$, $p < 0.05$, $d = 0.87$, respectively). Also, there was a significant main effect for trial block index for optode 1 ($F_{2,22.8} = 3.5431$, $p < 0.05$). Depicted below, Figure 5 represents the average activation for ALS and HC groups at optode 1 (left) and optode 7 (right). As expected, there is greater neural activation for the ALS group during the KDT compared to the HC group.

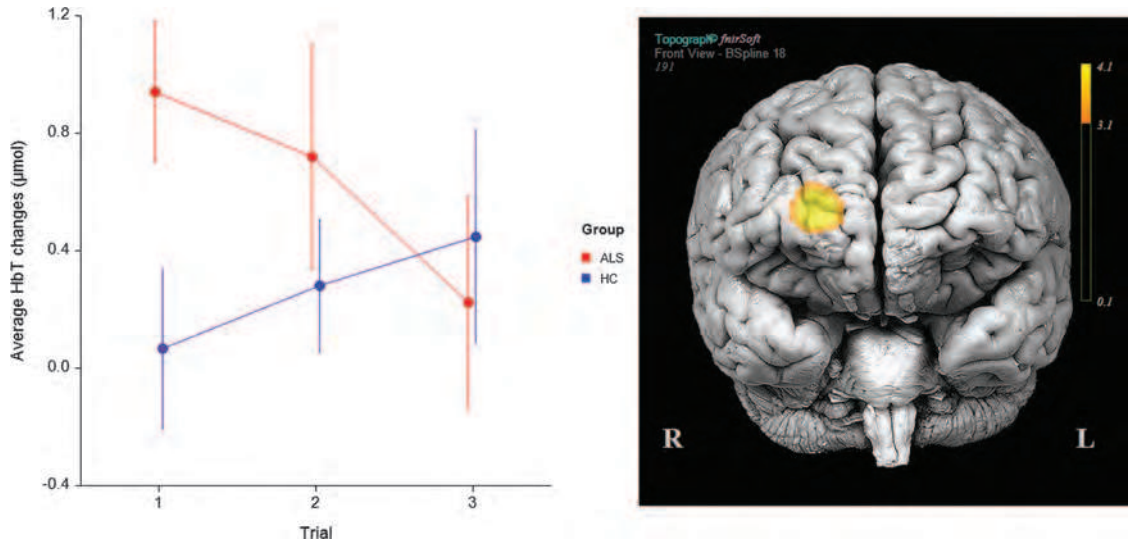

Fig. 3. Average total hemoglobin (HbT) changes at optode 12 for the NIT task across groups. Error bars are SEM. (left) Projection of F-statistics map on brain surface image marks significant area of interaction. Based on Ref. [53], BSpline interpolation was used to generate surface representation from f values (right).

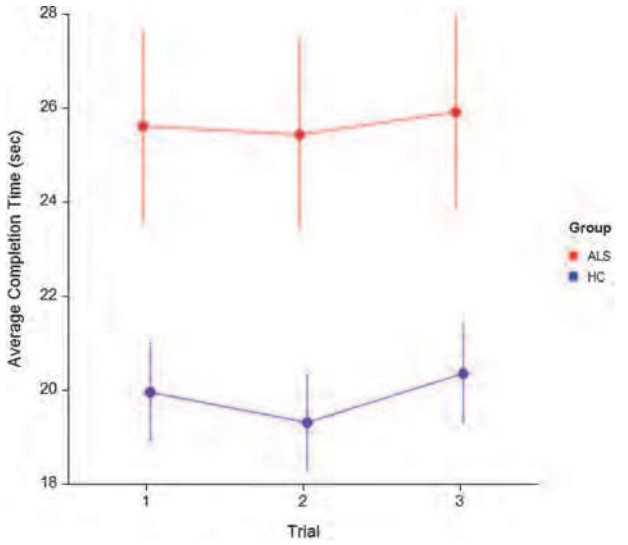

Fig. 4. Average completion time of KDT across groups. Error bars are SEM.

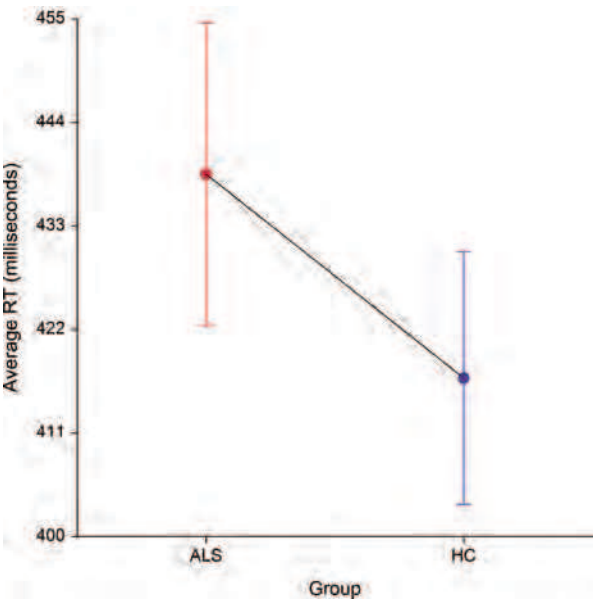

Fig. 6. Average response time (RT) for CPT task across groups with $d = 0.38$. Error bars are SEM.

CPT Task

Behavioral Measures

For the CPT task, the average RT for the ALS group was (mean + SD) 438.5 ± 66.25 milliseconds while the HC group was 416.82 ± 155.33 milliseconds with a small-to-moderate effect size ($d = 0.38$) which indicates that the ALS group was about 0.4 standard deviations slower in response time compared to the HC. Average accuracy for the ALS group was 0.99 ± 0.01 and for HC group, it was 0.99 ± 0.002. There was no difference for the average RT and accuracy in the CPT task across groups, although the ALS group seemed to have slightly higher average response times compared to HC (see Fig. 6). To determine if there was any temporal effect, as well as to remove the regression toward the mean effect, the CPT task was averaged in 10 epochs of 30 seconds each. No temporal differences were found when RT is averaged every 30 sec (10 epochs throughout the task) as shown in Figure 7 ($F_{1, 63.7} = 2.466$, $p > 0.1$).

fNIR Measures

There was a significant main effect for group on optode 14 ($F_{1, 29} = 3.976$, $p = 0.055$, $d = 1.01$) (see Fig. 8). The HbT difference between the ALS and HC groups showed a large positive effect ($d = 1.01$) indicating that the ALS group had a one standard deviation increase in HbT activation of the inferior frontal gyrus compared to the HC group. No other significant group differences were observed at any other optode for the CPT. Depicted in Figure 9, there was an interaction of group and epoch segments (10 epochs throughout the task) on optode 2 ($F_{9, 71.2} = 2.569$, $p < 0.05$). Also, there were main effects for epoch segments indicating that during performance of the CPT task there

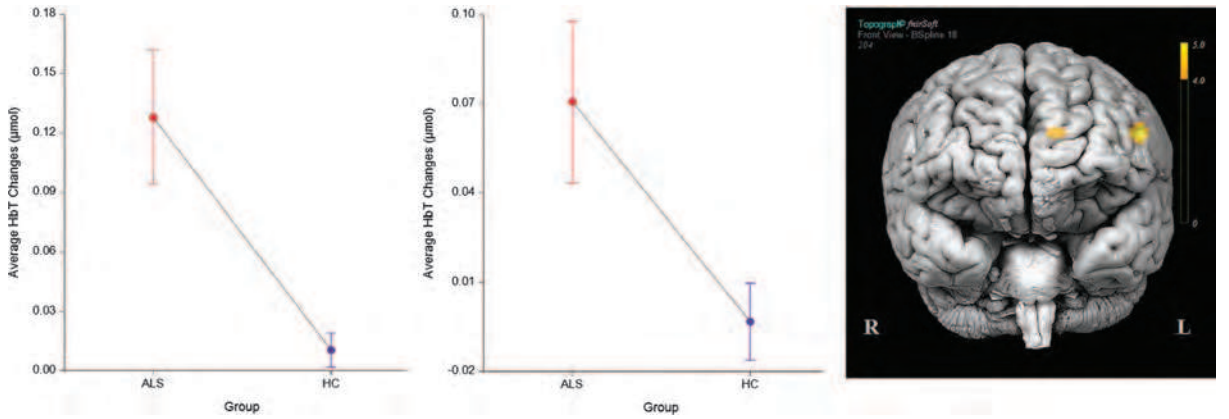

Fig. 5. Average total hemoglobin (HbT) changes for the KDT task of optode 1 (left) and optode 7 (middle) across groups. Error bars are SEM. Projection of F-statistics map on brain surface image marks significant areas (optodes 1 and 7). Based on [53], BSpline interpolation was used to generate surface representation from f values for comparison of group effect (right).

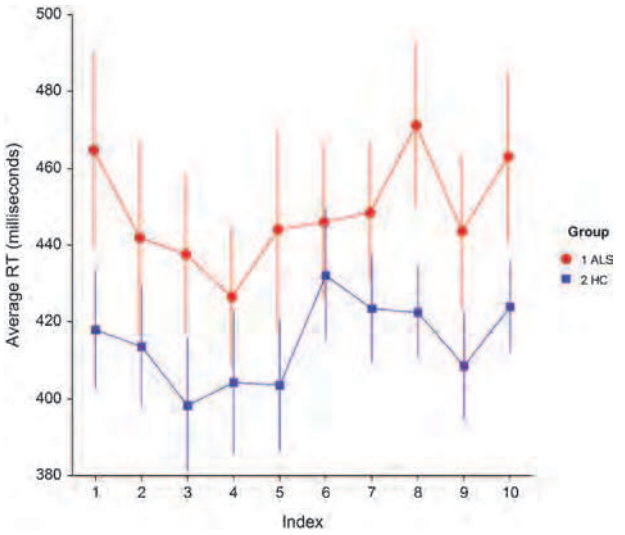

Fig. 7. Average response time (RT) for CPT task across groups throughout the task (10 epochs). Error bars are SEM.

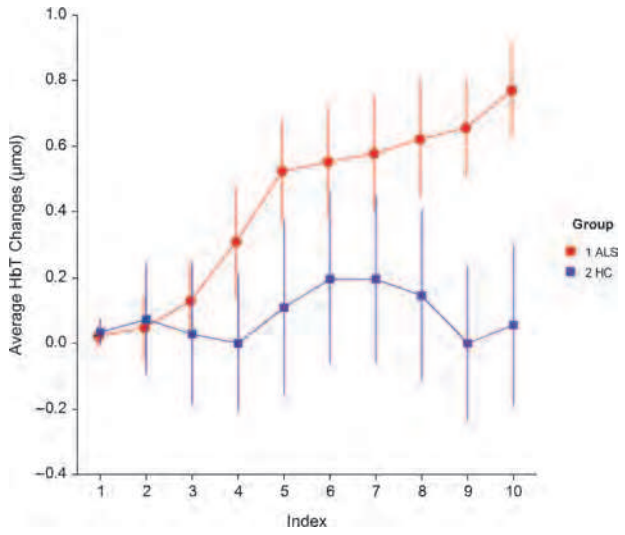

Fig. 9. Average HbT changes from beginning to end (10 epochs in total) for all groups. Error bars are SEM.

was an increase in activation of the lateral channels in both groups: optode 1 ($F_{9,4} = 7.948$, $p < 0.05$), optode 2 ($F_{9,71.2} = 4.577$, $p < 0.01$), optode 3 ($F_{9,61.7} = 2.113$, $p < 0.05$), optode 4 ($F_{9,57.4} = 2.167$, $p < 0.05$), optode 10 ($F_{9,76.4} = 9.895$, $p < 0.01$), optode 11 ($F_{9,64.7} = 5.605$, $p < 0.01$), optode 13 ($F_{9,82.1} = 9.470$, $p < 0.01$), optode 14 ($F_{9,4} = 7.204$, $p < 0.05$), optode 15 ($F_{9,4} = 7.204$, $p < 0.01$), and optode 16 ($F_{9,4} = 6.402$, $p < 0.05$). However, the ALS group has higher increases in HbT compared to the HC group as seen in Figure 9.

DISCUSSION

The main goal of this study was to assess if optical brain imaging can be used to capture cognitive task induced cortical hemodynamic differences in ALS patients and matching healthy controls. Optical brain imaging (fNIR) has seen a growing interest in recent years [42] and has already been utilized as a brain activation monitor in natural environments for a variety of applications such as working memory, attention, cognitive workload and learning/ training [38, 67]. Optical brain imaging has also been used to study cognitive dysfunction in clinical populations [50, 68, 69] including assessment of working memory function of ALS patients [53]. In this study, we focused on sustained attention and executive function in ALS patients using CPT, NIT and KDT tasks.

The significance of assessing cognitive and behavioral changes in ALS patients has been recognized by

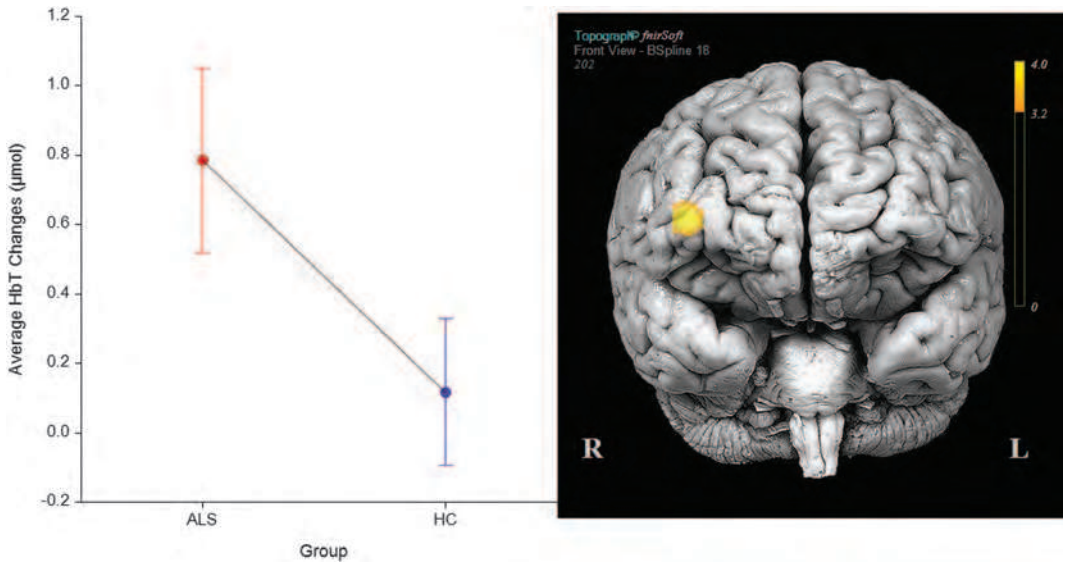

Fig. 8. Average total hemoglobin (HbT) activation changes for CPT task (mean of the task period) across groups. SEMs are reported as error bars (left). Projection of F-statistics map on brain surface image marks significant area (optodes 14). Based on Ref. [53], BSpline interpolation was used to generate surface representation from f values for comparison of group effect (right).

an increasing number of researchers and clinicians [5]. Understanding phenotypic variations and tracking progressive cognitive dysfunction can have important implications in symptom management and clinicopathological relationships.

Neuroimaging studies using continuous performance task has been used to study frontal brain areas mediating attention [70, 71]. In an fMRI study, Adler et al. (2011) reported increasing processing demand is associated with increased activation of attentional networks including the prefrontal cortex. The current study indicated that the average brain activation was different across the two groups (see Fig. 7) at optode 14 which is located in the right hemisphere close to AF8 in 10–20 international system (See Fig. 1), approximately at the inferior frontal gyrus. These data are consistent with prior research suggesting a specialized role involving the inferior frontal gyrus with attentional control [72, 73]. Considering that response time did not yield any differences across ALS and HC groups, (see Fig. 5), fNIR was sensitive enough to capture difference in the ALS group before the emergence of behavioral alterations. When temporal changes (i.e., dynamic trend) throughout the task were assessed by splitting the task into 10 epochs of 30 seconds each there continued to be no significant changes in RT (see Fig. 7). However, in brain activation assessments through fNIR, a different pattern was observed which showed an interaction for epoch segment and group (see Fig. 9). Again, the brain activation location was in the inferior frontal gyrus, at optode 2 which is located in the left hemisphere, and is contralateral to optode 14. These lateralized responses in ALS patients suggest that although there were not any differences in task performance (behavioral measures), the ALS group required greater brain activation (i.e., more neural resources) to maintain task demands compared to the healthy controls.

The NIT was a variation of Stroop task with three trials designed to elicit increasing cognitive demands for successful test performance. The increase in task complexity was clearly observed in the average response times for both ALS and HC groups (See Fig. 2-left) with a significant main effect for trials and a moderate to large effect size ($d = 0.59$) indicating over a half standard deviation slower response for the ALS group compared to the HCs. While there was a between-group difference in performance (Fig. 2-right), there was an elevated RT for the ALS group, relative to the HCs, across all three trials. As the difficulty in the NIT trials increased, there was a concomitant increase in the brain activation level in the HCs consistent with our previous studies [38, 74, 75], and described in other reports [76–78]. In contrast, the activation level was highest at the beginning of task performance (i.e., at trial 1) for the ALS group and decreased with subsequent trials. This progressive reduction in activation for the ALS group resulted in a significant interaction of trial and group. One interpretation of this interaction is that there is a higher neural cost of task initiation (i.e., 'warm up'). However, as the trials were not counter balanced based on difficulty level, it is plausible that a practice effect may have mitigated the need for increasing neural activation. Both factors, i.e., an order effect from easiest to most difficult task and practice effects may have resulted in a an inefficient state of cognitive processing at the NIT task inception for the ALS group.

Finally, the KDT is based on rapid number naming [59] and has been utilized as a practical and efficient determinant of head trauma and sports related concussion as the test is often administered on the sidelines during sport competitions or practices [58]. In this study, we utilized the KDT for assessing cognitive impairment in ALS patients. This is the first time the KDT has been implemented for cognitive impairment assessment in ALS patients. In terms of behavioral performance, there was a significant difference in average task completion time across ALS and HC groups (See Fig. 4). Also, fNIR data indicated higher activation in the lateral (optode 1) and medial (optode 7) prefrontal cortex regions for ALS patients compared to HC with large effect sizes ($d = 0.80$ and 0.87) for the respective areas. These hemodynamic activation region differences in the KDT are similar to the activation regions of the NIT and CPT for the ALS and HC samples. In addition, the effect sizes were large for the KDT and CPT as well as for the first trial of the NIT indicating ALS responses of 0.8 standard deviation units greater cognitive hemodynamic effort than the HC.

While our findings are exciting regarding understanding better the hemodynamic activation of the prefrontal cortex with the selected executive function tasks, our results must be interpreted with caution. A limitation of our work concerns the fact that not all areas of the brain that are involved in the task performances were measured with this fNIR technology. It is possible that due to plasticity and alterations in connectivity the mental workload was shifted to other areas of the brain during the trials of task performance. One likely area that was not monitored may be the parietal cortex. Also, it is important to note that the cognitive tasks were selected so as to not overwhelm patients with a debilitating illness such as ALS. It is possible we erred on the side of caution and that if more demanding tasks (such as tasks assessing working memory function) were administered, the ALS group might not be able recruit enough cognitive resources to keep up with the task requirements, thereby resulting in lower prefrontal cortex brain activation compared to the HC group. However, when we consider the behavioral performance evaluations for these three different cognitive tasks, the inclusion of the fNIR data provides preliminary evidence that ALS patients may, indeed, require higher cognitive resources than HC with increasing demand on attentional resources.

In summary, fNIR is a portable, safe, affordable and negligibly intrusive optical brain monitoring technology

that can be used to measure hemodynamic changes in the prefrontal cortex. These initial results indicate that fNIR can capture differences in brain activation of ALS patients in outpatient settings and everyday environments. Our results and work emphasize the potential of fNIR as a clinical tool in monitoring progression of neurocognitive effort and in some instances decline in populations such as persons affected with ALS.

Disclosure

fNIR Devices, LLC manufactures the optical brain imaging instrument and licensed IP and know-how from Drexel University. H. Ayaz and B. Onaral were involved in the technology development and thus offered a minor share in the new startup firm fNIR Devices, LLC.

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