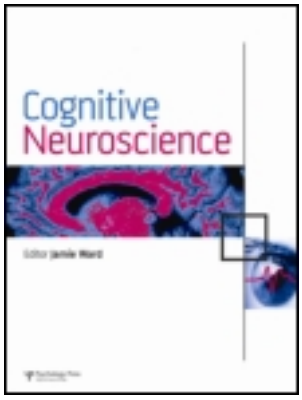

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Neural correlates of cognitive decline in ALS: An fNIRS study of the prefrontal cortex

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Neural correlates of cognitive decline in ALS: An fNIRS study of the prefrontal cortex

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Functional near infrared spectroscopy (fNIRS) is a clinically feasible functional neuroimaging modality for detecting early cortical changes due to neurodegenerative diseases that affect cognition. The objective of this preliminary investigation was to test for reduced prefrontal activity in persons with cognitive impairments due to amyotrophic lateral sclerosis (ALS). Participants were required to complete two N-back working memory tasks of increasing complexity during fNIRS recordings. Five participants with ALS and age- and gender-matched healthy participants comprised the experimental and control groups, respectively. Significant reductions in prefrontal oxygenation levels were observed for the left and right hemispheres in the ALS group compared to the control group. Reduced prefrontal activation despite intact behavioral performance for a working memory task may suggest early neuroanatomical, neurophysiological and/or compensatory mechanisms in affected individuals. The fNIRS-derived oxygenation measure shows promise as a sensitive neural marker to identify early neuropsychological impairments due to ALS.

Keywords: ALS; Cognition; fNIRS; Functional near infrared spectroscopy; N-back.

Until recently, neuronal loss from amyotrophic lateral sclerosis (ALS) was thought to be confined to the corticomotor pathways. Neuroimaging findings, however, have confirmed neurodegenerative changes that extend into the prefrontal and frontotemporal cortical networks (Abe et al., 1997; Abe, 2000; Abrahams et al., 1995; Abrahams et al., 2000). These changes are thought to underlie the wide range of cognitive deficits that have been associated with ALS (Abrahams et al., 2004; Abrahams et al., 2000; Wicks et al., 2008). The extant research has primarily focused on cognitive impairments due to ALS-frontotemporal dementia (ALS-FTD), whereas research on cortical functioning in non-demented individuals diagnosed with ALS is limited. An improved understanding of the cognitive endophenotypes associated with ALS

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will have a major impact on patient care, experimental drug trials, and targeted gene therapies for ALS (Azzouz, 2006; Bruijn, Miller, & Cleveland, 2004).

Imaging modalities may be particularly effective for improving knowledge about the neurological basis of cognitive impairments in ALS and for identifying neural-based diagnostic markers of the disease. Structural magnetic resonance imaging studies have revealed associations between gray and white matter loss associated with cognitive impairments (Gorno-Tempini et al., 2004; Mezzapesa et al., 2007). Although functional imaging studies have received less attention, functional magnetic resonance imaging and positron emission tomography are known to be sensitive to ALS-related changes in cortical functioning. For example, hypoperfusion in the frontal and temporal areas has been associated with working memory and verbal fluency deficits in non-demented individuals diagnosed with ALS (Abrahams et al., 2004; Abrahams et al., 2000; Hammer et al., 2011; Mantovan et al., 2003). Further advances in the endophenotyping of ALS and associated cognitive impairments will require the use of functional neuroimaging technologies that are widely accessible, affordable, and non-invasive.

Currently, the diagnosis of cognitive impairments in non-demented individuals with ALS relies on standardized neuropsychological assessments. The sensitivity of these assessments in early detection of mild cognitive impairments, however, is not well established. Because of the delay in diagnosing cognitive impairments, the timing of these deficits relative to motor impairments is poorly understood. There is some evidence that changes to extra-motor frontal regions precede or coincide with the onset of spinal (trunk and limb movement) or bulbar (speech and swallowing) symptoms; very rarely are cognitive changes seen after the onset of motor symptoms (Abrahams, Leigh, & Goldstein, 2005). Therefore, the early detection of cognitive changes in affected individuals has the potential to expedite the diagnosis of ALS and to predict the onset of related functional declines. Functional imaging results are now used to support the diagnosis of FTD; similar functional imaging-derived analysis techniques may expedite the diagnosis of ALS and related neuropsychological impairments.

The primary objective of this preliminary investigation was to test for reduced prefrontal activity in persons with cognitive impairments due to ALS using fNIRS. To our knowledge, fNIRS has not been used to study cortical functioning in ALS. This technology is particularly well suited for widespread clinical use because it is affordable, portable, and non-invasive. Previous research has demonstrated the adequacy of fNIRS for registering systematic variations in oxygenated hemoglobin levels from the prefrontal cortex in response to working memory and intentional load (Ayaz et al., 2012; Ayaz, Willems et al., 2010; Izzetoglu et al., 2004). These results support previous findings that neurons in the dorsolateral prefrontal cortex and medial prefrontal cortex are actively engaged in working memory and attention processes (McCarthy et al., 1994; Smith & Jonides, 1997). Because fNIRS-derived hemodynamic responses rely on tight neurovascular coupling in cortical regions, affected neurons would presumably show abnormal cortical hemodynamic responses because of disruptions to neurovascular coupling.

METHODS

Participants

A total of 10 participants volunteered for the study. Five individuals with ALS (three male, two female) and five age- and gender-matched neurologically non-impaired healthy participants (three male, two female) were recruited. Mean chronological age of the ALS group was 60.2 years (*SD*: 15.09, range: 44–79). Mean age of healthy participants was 59.2 years (*SD*: 14.13, range: 41–80). The ALS functional rating scale-revised (ALSFRS-R) and the Montreal cognitive assessment (MoCA) were used to assess motor and cognitive performance, respectively (see Table 1 for participant details).

Experimental tasks

Participants were required to complete a computerized version of the N-back test of working memory at two levels of increasing complexity, namely the 1- and 3-

TABLE 1
Demographic details for all participants with ALS included in the study

ID	*Gender*	*Age*	*Loci of onset*	*MoCA score*	*ALSFRS-R score*
1	M	50	Cervical, Lumbar	25	25
2	M	44	Cervical	23	30
3	M	73	Cervical	20	46
4	F	55	Lumbar	23	40
5	F	79	Bulbar	22	43

back tasks; the N-back has previously been shown to be sensitive to working memory deficits in persons with ALS (Hammer et al., 2011). During the task, participants were required to attend to a sequence of letters of the alphabet presented one at a time and determine if the final letter shown was the same as the last or third from last letter in the sequence for the 1- and 3-back tasks, respectively.

Experimental protocol

Prior to testing, participants were provided one practice trial for the 1- and 3-back tasks to mitigate the effect of task novelty. The following epochs were recorded during data collection (1) a pre-task baseline of 20 seconds at the beginning of each task while participants were asked to relax with closed eyes (2) instructions for the task were provided by the researcher and (3) the task was administered and completed. The inter-stimulus interval was 1000 milliseconds and each stimulus was presented on the screen for 1000 milliseconds. Three blocks of each N-back task were recorded from each participant. One block of tasks consisted of five trials each of the 1- and 3-back tasks. The order of presentation was randomized within and across blocks for each participant. Participants were given explicit instructions to limit excessive head/neck movement and facial muscle contraction in order to minimize motion artifacts.

Responses for the N-back task were recorded in real-time by a research assistant. For each N-back task, a total score of 5 correct responses was possible within a single block and a total of 15 correct responses for three blocks. Each correct response was given a score of 0 and an incorrect response a score of 1; therefore, a higher value indicates lower response accuracy for the task.

Instrumentation

A 16 channel fNIRS system was used. Eight channels each are located over the left and right prefrontal cortices (see Figure 1). The head array consists of four Light Emitting Diodes (LEDs) that emit light at three different wavelengths (730nm, 805nm, and 850nm) in the near-infrared spectrum. It also houses 10 light detectors that are positioned 2.5cm from the nearest emitter. The head array was secured to the participants' foreheads using a Velcro head strap. The head array was placed on each individual forehead with an attempt to align the bottom row of the detectors with one of the sites f_{P1}, f_{pz}, and f_{P2} from the International 10–20 system. The sampling rate for data acquisition was 2Hz (see Ayaz et al., 2011 and Ayaz et al., 2012, for more details on instrumentation and working principles).

Data processing and analysis

A visual analysis program, fnirSoft (Ayaz, 2010) was used to process the fNIR data. The raw light intensity measures were filtered using a low pass filter (cut off frequency = 0.1Hz). Signal quality and motion artifact contaminated channels were identified by using a sliding window motion artifact rejection (SMAR) algorithm that is provided with the fnirSoft (Ayaz, Izzetoglu et al., 2010). Next, the modified beer lambert law was used to convert the raw light intensity measure to oxy and deoxy Hb concentration changes. Average oxygenation levels (difference of oxy Hb – deoxy Hb) were expressed relative to the pre-task baseline for each N-back task.

Screening assessments

The MoCA, a cognitive screening tool, designed to detect mild cognitive impairment was administered to identify cognitive impairments in the ALS and control groups. The test assesses different cognitive domains including executive function, orientation, visuospatial, memory, and language function (Nasreddine et al., 2005). All participants were required to complete the MoCA before the fNIRS recordings. A total score of 30 is possible with scores below 26 considered indicative of cognitive impairment.

The ALSFRS-R is a validated rating scale developed to monitor functional decline in patients with ALS (Cedarbaum et al., 1999). The ALSFRS-R includes 12 questions revolving around common tasks. Each task is rated on a 5-point scale; a total of 48 points is possible with higher scores indicating less functional impairment.

Statistical analysis

The mean oxygenation levels in the left and right hemisphere for the ALS and controls groups were compared using a repeated measures analysis of variance (ANOVA) test. The repeated measures ANOVA was also used to determine between- and within-group task effects for the 1- and 3-back tasks. Furthermore, main and interaction effects for group and task were determined for each channel. False discovery rate (FDR) correction was applied and a q-value of .01 was adopted for significance testing (Benjamini &

Hochberg, 1995). Differences in behavioral responses for the N-back tasks between the ALS and control groups were determined using repeated measures ANOVA. In addition, a *t*-test was used to determine group differences for the MoCA.

RESULTS

Statistical analysis was performed on the oxygenation data from the five participants with ALS and five age- and gender-matched healthy participants. Both left and right hemisphere oxygenation (oxy Hb – deoxy Hb) were analyzed and are included in this preliminary report. Significant results were obtained only for channels 5 and 10 and are reported in the following sections (refer to Figure 1 for channel location).

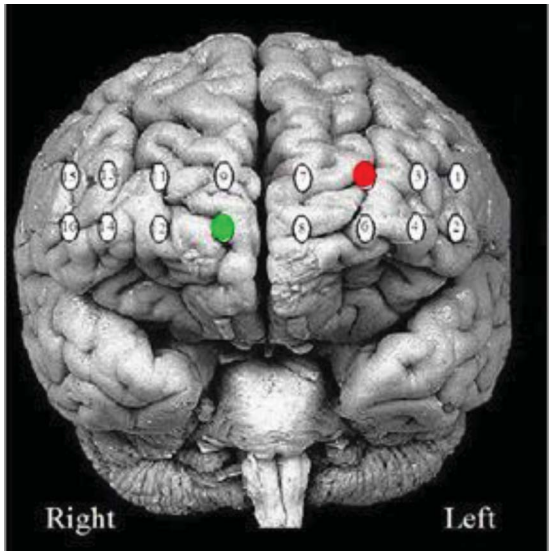

Figure 1. Approximate location of fNIRS channels over the prefrontal cortex. Channel 5 (red) located over the left hemisphere and channel 10 (green) over the right hemisphere.

Group effects across N-back tasks

A significant effect for group was observed only in the left hemisphere [$F(1, 24) = 8.56$, $p < .01$], with the control group displaying greater oxygenation levels compared to the ALS group (see Figure 2a). Similar group oxygenation differences were obtained for a single left hemisphere [$F(1, 52) = 5.93$, $p = .045$] and right hemisphere channel [$F(1, 52) = 4.40$, $p = .07$] (see Figure 2b).

Group × task interaction effects

A significant group × task interaction was observed in the left hemisphere [$F(3, 69) = 2.96$, $p = .038$] and right hemisphere [$F(3, 69) = 3.28$, $p = .027$]. Post-hoc tests showed a significantly greater activation for the 3-back task in the control group compared to activation for 1- and 3-back tasks in the ALS group for both hemispheres. Within the control group, oxygenation levels were greater for the 3-back task compared to the 1-back task for both hemispheres (see Figure 3a for left hemisphere and 3b for right hemisphere results). A significant group × task interaction was also observed for channel 5 [$F(2, 52) = 14.04$, $p < .001$] and channel 10 [$F(2, 52) = 5.60$, $p < .05$].

Accuracy of behavioral responses

Significant group differences were observed for MoCA scores with the control group achieving higher scores than the ALS group [$t(7) = -3.61$, $p < .01$].

The accuracy of the N-back responses did not differ significantly between the control and ALS groups [$F(1, 28) = 2.15$, $p = .15$] (see Table 2 for mean and *SD* of MoCA scores and inaccurate responses for each group).

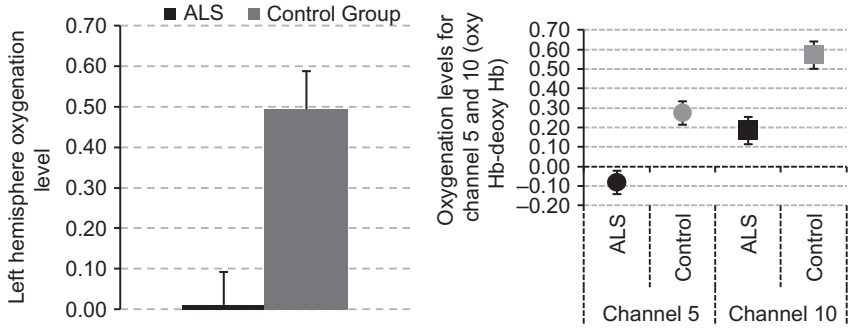

Figure 2. (a) Significant differences between the ALS and control for left hemisphere (channels 1–8) oxygenation levels; (b) Oxygenation levels for channel 5 and channel 10 show significant group differences; error bars represent standard error of mean.

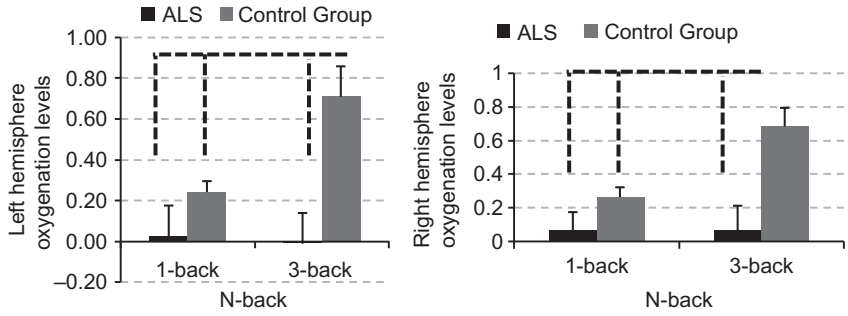

Figure 3. (a) Significant differences in left hemisphere (channels 1–8) oxygenation levels between the ALS 1- and 3-back tasks compared to the 3-back task of the control group; (b) Significant differences in right hemisphere (channels 9–16) oxygenation levels between the ALS 1- and 3-back tasks compared to the 3-back task of the control group; bold dotted lines indicate significant task differences between the groups. Within group differences were observed for the control group with greater oxygenation levels for the 3-back compared to the 1-back task (indicated by bold dotted lines).

TABLE 2
Mean and *SD* of MoCA scores and behavioral responses for the N-back tasks for each group

			N-back scores			
	MoCA scores		*1 back*		*3 back*	
Group	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
ALS	22.6	1.82	0.27	0.46	0.73	1.03
Control	26.3	0.96	0.27	0.80	0.20	0.41

DISCUSSION

In this investigation, we recorded brain activity levels from the prefrontal cortex using fNIRS in non-demented persons with ALS to identify potential neurological correlates of measurable cognitive deficits. The major finding in this study was that, in comparison to that of the healthy controls, the left and right hemisphere oxygenation levels of those with ALS were significantly reduced and not affected by task difficulty. The reduced activity was most evident for channels 5 and 10, located approximately over the medial prefrontal cortex in the left and right hemispheres, respectively. The current findings are consistent with previous investigations on persons with ALS showing hypometabolism and reduced activation in prefrontal regions in response to demands on working memory (Abrahams et al., 2004; Hammer et al., 2011). This study adds to this prior literature by demonstrating attenuated prefrontal activation *prior* to detectible declines in working memory. These findings suggest that the observed changes in cortical activity are not specifically linked to working memory deficits but rather to early prefrontal neurodegenerative changes. An alternative explanation is that the decreased oxygenated hemoglobin levels are precursors to later appearing declines in working memory.

Attenuated oxygenation levels may be indicative of prefrontal neuronal loss

The decreased oxy hemoglobin levels in the left and right hemispheres in the ALS group provides additional evidence of neuronal degeneration outside of the motor system, specifically the prefrontal cortex. Spongiform degeneration of the prefrontal and temporal cortices has been reported in individuals with ALS-FTD (Neary, Snowden, & Mann, 2000; Snowden, Neary, & Mann, 2002); decreased cortical thickness and grey matter volume in the frontal and temporal cortices including the prefrontal cortex have been reported in a group of patients with mild cognitive impairments (Witiuk, 2011). Although the effects of neuronal loss on neurovascular coupling are poorly understood, decreased oxygenation levels might be expected if neuronal degeneration results in diminished blood supply. More research is needed to understand the effects of neuronal deterioration on neurovascular coupling.

Neurophysiologic capacity limitations with increasing cognitive workload in ALS

The reduced activation levels observed for both the 1-back and 3-back tasks in the participants with ALS were in contrast to the expectation of increasing activation with increasing cognitive workload, which was observed in our control participants and in prior fNIRS studies (Ayaz et al., 2010; Ayaz et al., 2012; Izzetoglu et al., 2005). This finding raises the possibility that the 3-back task exceeded the frontal processing capabilities in these participants. This interpretation is supported by research on healthy participants showing attenuated prefrontal activation during excessive demands of stimulus processing and response selection

(Dhankhar et al., 1997; Goldberg et al., 1998; Price et al., 1992). Despite these presumed neurophysiologic limitations to prefrontal regions, the behavioral performance in the ALS group indicates possible compensatory recruitment of surrounding cortical areas during the task. Specifically, their task performance may have benefited from compensatory reorganization and resource reallocation to other cortical regions in order to meet cognitive demands when prefrontal neurons degenerate (Konrad et al., 2002; Lulé, Ludolph, & Kassubek, 2009). Future studies using full head NIRS systems capable of recording hemodynamic responses from several cortical regions will be able to shed light on compensatory mechanisms in ALS.

Cognitive load-dependent change in prefrontal oxygenation levels

The observed association between prefrontal oxygenation levels and task difficulty (i.e., 1-back vs. 3-back) in the control participants is consistent with the findings of other fNIRS studies that have observed cognitive load-related increase in oxygenation levels (Ayaz et al., 2012; Ayaz et al., 2007; Izzetoglu et al., 2005). The medial prefrontal cortex, the approximate location of optodes 5 and 10, have been linked to working memory and cognitive workload-related processes in healthy individuals (for reviews see d'Esposito et al., 1998; Owen, 1997). Increased cognitive effort from the 1- to 3-back task in the control group may have benefited behavioral performance which was comparable between the two tasks.

CONCLUSIONS

Reduced prefrontal activity specifically over the medial prefrontal cortex in non-demented individuals with ALS may be an early indicator of subsequent cognitive impairments and/or executive dysfunction in these individuals. These preliminary fNIRS findings are consistent with PET and fMRI studies showing attenuated prefrontal activation. Our results indicate that fNIRS-derived oxygenation measures may be a sensitive neural marker for detecting early neurodegenerative changes. A longitudinal follow-up on a larger group of affected individuals using a range of neuropsychological tasks will provide further information needed to understand the relations between neuronal loss and cognitive decline due to ALS.

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REFERENCES

Abe, K. (2000). Cognitive function in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders : Official Publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases*, *1*, 343–347.

Abe, K., Fujimura, H., Toyooka, K., Sakoda, S., Yorifuji, S., & Yanagihara, T. (1997). Cognitive function in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *148*(1), 95–100.

Abrahams, S., Goldstein, L., Simmons, A., Brammer, M., Williams, S., Giampietro, V., & Leigh, P. (2004). Word retrieval in amyotrophic lateral sclerosis: A functional magnetic resonance imaging study. *Brain*, *127*, 1507–1517.

Abrahams, S., Leigh, P. N., & Goldstein, L. H. (2005). Cognitive change in ALS: A prospective study. *Neurology*, *64*, 1222–1226. doi: 10.1212/01.WNL.0000156519.41681.27

Abrahams, S., Leigh, P. N., Harvey, A., Vythelingum, G. N., Grise, D., & Goldstein, L. H. (2000). Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia*, *38*, 734–747.

Abrahams, S., Leigh, P. N., Kew, J. J., Goldstein, L. H., Lloyd, C. M., & Brooks, D. J. (1995). A positron emission tomography study of frontal lobe function (verbal fluency) in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences*, *129*(Suppl.), 44–46.

Ayaz, H. (2010). *Functional Near Infrared Spectroscopy based Brain Computer Interface* (PhD Thesis). Drexel University, Philadelphia, PA.

Ayaz, H., Izzetoglu, M., Bunce, S., Heiman-Patterson, T., & Onaral, B. (2007). Detecting cognitive activity related hemodynamic signal for brain computer interface using Functional Near Infrared Spectroscopy. *Neural Engineering, 2007. CNE'07. 3rd International IEEE/EMBS Conference*, pp. 342–345.

Ayaz, H., Izzetoglu, M., Shewokis, P. A., & Onaral, B. (2010). Sliding-window motion artifact rejection for functional near-infrared spectroscopy. *Conference Proceedings IEEE Engineering in Medicine Biology Society*, 6567–6570.

Ayaz, H., Shewokis, P. A., Bunce, S., Izzetoglu, K., Willems, B., & Onaral, B. (2012). Optical brain monitoring for operator training and mental workload assessment. *Neuroimage*, *59*(1), 36–47.

Ayaz, H., Shewokis, P. A., Curtin, A., Izzetoglu, M., Izzetoglu, K., & Onaral, B. (2011). Using MazeSuite and Functional Near Infrared Spectroscopy to study learning in spatial navigation. *Journal of Visual Experiments* (56), e3443.

Ayaz, H., Willems, B., Bunce, B., Shewokis, P. A., Izzetoglu, K., Hah, S., & Onaral, B. (2010). Cognitive workload assessment of air traffic controllers using optical brain imaging sensors. In T. Marek, W. Karwowski, & V. Rice (Eds.), *Advances in understanding human performance: Neuroergonomics, human factors design, and special populations* (pp. 21–31). CRC Press Taylor & Francis Group.

Azzouz, M. (2006). Gene therapy for ALS: Progress and prospects. *Biochimica Et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1762*, 1122–1127.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 289–300.

Bruijn, L. I., Miller, T. M., & Cleveland, D. W. (2004). Unraveling the mechanisms involved in motor neuron degeneration in ALS. *Annual Review of Neuroscience*, *27*, 723–749.

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., & Nakanishi, A. (1999). The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*, *169*(1), 13–21.

d'Esposito, M., Aguirre, G., Zarahn, E., Ballard, D., Shin, R., & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Cognitive Brain Research*, *7* (1), 1–13.

Dhankhar, A., Wexler, B. E., Fulbright, R. K., Halwes, T., Blamire, A. M., & Shulman, R. G. (1997). Functional magnetic resonance imaging assessment of the human brain auditory cortex response to increasing word presentation rates. *Journal of Neurophysiology*, *77*, 476–483.

fNIRS - fNIR system 200 [Apparatus]. (2009). Potomac MD, fNIR Devices LLC.

Goldberg, T. E., Berman, K. F., Fleming, K., Ostrem, J., Van Horn, J. D., Esposito, G., & Weinberger, D. R. (1998). Uncoupling cognitive workload and prefrontal cortical physiology: A PET rCBF study. *Neuroimage*, *7*, 296–303.

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., & Miller, B. L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology*, *55*, 335–346.

Hammer, A., Vielhaber, S., Rodriguez-Fornells, A., Mohammadi, B., & Münte, T. F. (2011). A neurophysiological analysis of working memory in amyotrophic lateral sclerosis. *Brain Research*, *1421*, 90–99.

Izzetoglu, K., Bunce, S., Onaral, B., Pourrezaei, K., & Chance, B. (2004). Functional optical brain imaging using near-infrared during cognitive tasks. *International Journal of Human-Computer Interaction*, *17*(2), 211–227.

Izzetoglu, M., Izzetoglu, K., Bunce, S., Ayaz, H., Devaraj, A., Onaral, B., & Pourrezaei, K. (2005). Functional near-infrared neuroimaging. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, *13* (2), 153–159.

Konrad, C., Henningsen, H., Bremer, J., Mock, B., Deppe, M., Buchinger, C., & Brooks, B. (2002). Pattern of cortical reorganization in amyotrophic lateral sclerosis: A functional magnetic resonance imaging study. *Experimental Brain Research*, *143*(1), 51–56.

Lulé, D., Ludolph, A. C., & Kassubek, J. (2009). MRI-based functional neuroimaging in ALS: An update. *Amyotrophic Lateral Sclerosis*, *10*(5–6), 258–268.

Mantovan, M., Baggio, L., Barba, G. D., Smith, P., Pegoraro, E., Soraru, G., & Angelini, C. (2003). Memory deficits and retrieval processes in ALS1. *European Journal of Neurology*, *10*(3), 221–227.

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., & Shulman, R. G. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences*, *91*, 8690–8694.

Mezzapesa, D., Ceccarelli, A., Dicuonzo, F., Carella, A., De Caro, M., Lopez, M., & Simone, I. (2007). Whole-brain and regional brain atrophy in amyotrophic lateral sclerosis. *American Journal of Neuroradiology*, *28*(2), 255–259.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., & Chertkow, H. (2005). The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*, 695–699.

Neary, D., Snowden, J., & Mann, D. (2000). Cognitive change in motor neurone disease/amyotrophic lateral sclerosis (MND/ALS). *Journal of the Neurological Sciences*, *180*(1), 15–20.

Owen, A. M. (1997). Cognitive planning in humans: Neuropsychological, neuroanatomical and neuropharmacological perspectives. *Progress in Neurobiology*, *53*, 431–450.

Price, C., Wise, R., Ramsay, S., Friston, K., Howard, D., Patterson, K., & Frackowiak, R. (1992). Regional response differences within the human auditory cortex when listening to words. *Neuroscience Letters*, *146*(2), 179–182.

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology*, *33*(1), 5–42.

Snowden, J. S., Neary, D., & Mann, D. M. A. (2002). Frontotemporal dementia. *The British Journal of Psychiatry*, *180*(2), 140–143.

Wicks, P., Turner, M. R., Abrahams, S., Hammers, A., Brooks, D. J., Leigh, P. N., & Goldstein, L. H. (2008). Neuronal loss associated with cognitive performance in amyotrophic lateral sclerosis: An (11C)-flumazenil PET study. *Amyotrophic Lateral Sclerosis: Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases*, *9*(1), 43–49.

Witiuk, K. (2011). *Investigating cognitive impairments in amyotrophic lateral sclerosis (ALS) using eye movements and functional magnetic resonance imaging (fMRI)*. (Unpublished Master of Science). Canadian theses, Ontario, Canada.