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USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY TO MEASURE COGNITIVE FUNCTION: WHEN WILL IT BECOME AN ACCEPTED CLINICAL TOOL FOR COGNITIVE AGING AND PRODROMAL DEMENTIA SCREENING?*

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This article presents a historical perspective of foundational studies utilizing near-infrared spectroscopy (NIRS) to measure the hemodynamics, oxygenation, and activation of the human brain cortex during cognitive tasks, called functional NIRS (fNIRS). It discusses studies representative of the diagnostic power and potential that fNIRS has shown for providing increased understanding of cognitive changes with aging and dementia. It concludes by discussing challenges that continue to confront the implementation of NIRS and fNIRS in clinical and translational research, in particular, the challenges to measure cognitive function and impairment in aged, chronically ill, and fragile subjects with or without dementia. It is written specifically in memoriam, honoring Britton Chance, therefore papers authored by him and his collaborative research family are weighted to illustrate the significant foundation and legacy he has left to this world.

Keywords: Cerebral blood oxygenation; oxyhemoglobin; neural activation.

1. Introduction

Near-infrared spectroscopy (NIRS) is an optical method that measures changes in the concentration of oxygenated hemoglobin [HbO_2] and deoxygenated hemoglobin [Hb] in the microvascular bed of tissue. It has been almost 30 years since the original pioneering studies applying NIRS to measure the redox biochemistry, hemodynamics, oxygenation, and activation of the human brain cortex during tasks, called functional NIRS (fNIRS).[1–6] There are now hundreds of studies applying fNIRS, leaving no doubt that neural function has a vascular correlate that produces hemodynamic ripples, tissue oxygenation changes and metabolic by-products.

*This paper is written in tribute and remembrance of Britton Chance, with gratitude for his mentorship, friendship, and youthful heart.

These signals are biomarkers for important physiological and neurocoupling events such as neural activation, vasoreactivity, and compensatory vascular reserve of the brain. The potential and utility of NIRS and fNIRS are evident, yet this neuroimaging technique has been slow to progress to a validated clinical tool and remains used mostly at the research level.

Enthusiasm for fNIRS and NIRS is based on the hopes of applying it to better understand a spectrum of problems such as neurological diseases, birth defects, cognitive delay, learning disability, dementia, head trauma, neuro-rehabilitation of stroke, depression, and psychosis. The non-invasiveness and possible cost-effectiveness of fNIRS relative to other neuroimaging techniques make it an excellent candidate for use as a complimentary technology and clinical tool for assessing cognitive function. It allows a degree of portability unavailable with the commonly used imaging modalities such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), and single-photon emission computed tomography, (SPECT). fNIRS requires neither injection of contrast dyes or exposure to radiation like PET and SPECT nor does it require the subject to lie in a tube, motionless for long periods necessary for PET, SPECT, and fMRI. With fMRI, the subject must endure periods of loud banging noise. NIRS is safe to use with infants, children, and frail elders, and because it requires no contrast agents, it is safe for people with kidney disease (common in the elderly) for whom contrast agents can be toxic. Even the most advanced fNIRS systems fit into the space of an examination room with real-time display via laptop computer.

The 2010 World Alzheimer Report estimates about 35 million people have dementia worldwide and that figure is likely to double every 20 years, to nearly 66 million in 2030 and 115 million in 2050. The global cost of dementia will likely exceed $604 billion in 2011, or 1% of the world's gross domestic product.[7] Can NIRS and fNIRS biomarkers provide early identification of those at risk for mild cognitive impairment (MCI) or measure its progression to dementia? From what we have learned so far, can the increased knowledge or understanding provided by the addition of fNIRS neuroimaging and functional mapping translate to improved differential diagnostic accuracy during early stages of cognitive difficulties? Does the information translate to better outcomes for those afflicted? Will optical imaging ever become the clinical or bedside tool envisioned by its beloved and pioneering forefathers?

This article presents a historical perspective of foundational studies utilizing fNIRS. It proceeds to briefly discuss studies representative of the diagnostic power and potential that fNIRS has shown for providing increased understanding of cognitive changes with aging. It aims to address the above questions and concludes with outlining the challenges that continue to confront the implementation of NIRS and fNIRS in clinical and translational research. In particular, challenges of fNIRS to measure cognitive function and impairment in aged, chronically ill, fragile subjects with dementia are discussed.

This article is written specifically in memoriam, honoring Britton Chance, therefore papers authored by him and his collaborative research family are weighted to illustrate the significant foundation he has left to this world. His global collaboration with an interdisciplinary team of researchers, working to quantify NIR optical characteristics and producing a more robust picture of tissue oxygen saturation in a host of diseases and tissues, has spearheaded and driven the bioimaging field to new frontiers.

2. Methods

A literature search in MEDLINE was performed combining the key word search for near-infrared spectroscopy, NIRS, functional NIRS, fNIRS, dementia, fMRI and brain aging. Inclusion criteria for the literature search were limited to English language. The results of the search identified 2,252 manuscripts. The selected manuscripts were restricted to studies and instrumentation applicable to brain and cognition measurements published up to May 2011. The full texts of 169 publications were retrieved and reviewed. Next, the references of the selected papers were reviewed for suitable literature not found by MEDLINE search. Cited references were selected based on historical significance, co-authorship by Britton Chance to commemorate his legacy through review of his scientific work in cognition, demonstration of the diagnostic potential, and discussion of challenges that continue to confront the implementation of NIRS and fNIRS in clinical and translational research to measure cognitive function in aging. It is not an exhaustive review of fNIRS in dementia.

3. Foundational Studies in fNIRS

In 1977 Jöbsis, using techniques for optical monitoring of intact tissues, he learned as a postdoctoral student in Britton Chance's lab, described the application of NIRS to measure hemoglobin signals in the intact cat brain during whisker stimulation.[1] The significance of this new development was apparent and a rapid succession of subsequent pioneering studies followed, such as those in the preterm infant,[2] neonates,[3] and adults.[4−6,8−11] They sparked an exciting and novel approach to noninvasive cerebral monitoring and expanded the application of NIRS to study cerebral cortex activation during motor, visual or cognitive tasks. Modulating the NIR light in time domain[12] or phase,[5] along with animal studies, theoretical models, and mathematical algorithms, allowed validated quantitation of oxygenation, metabolism, and blood hemodynamics.[13]

3.1. *The classical response to neural activation and cognition*

Fortuitously, early single-site fNIRS studies, using a protocol of 60 s duration measuring the occipital cortex during visual simulation, the parietal motor cortex during rapid finger tapping, and the prefrontal cortex (PFC) during a cognitive task, demonstrated that simple cognitive activation produced a strong hemodynamic response, usually resulting in increased total regional cerebral blood volume (rCBV), increased regional cerebral blood oxygenation, (rCBO) and excess [HbO_2], with concomitant reduction in [Hb] coined "luxury perfusion".[10,11,14] This response correlated well with the Blood Oxygen Level−Dependent (BOLD) signal measured by fMRI confirming validity of the fNIRS signal.[15] An increase in [HbO_2] in conjunction with task performance is often considered the "classical" or typical response to neural activation and the presence, percentage change, and regional patterns of CBO during a task are the fundamental signals of activation that are used to evaluate cognitive function in the cerebral cortex. The reproducibility and validated interpretation of these signal variables are critical in allowing clinicians to have confidence in the ability of fNIRS to identify biomarkers of pathology related to dementia.

Chance *et al.*[11,14] reported that in contrast to neuronal firing seen in exposed brain tissue that occurs in milliseconds, the fNIRS signal sees a later slow response taking more than a second, can evolve over 10−12 s and has a gradual reversal of oxygenation to baseline levels, often taking up to 2 min. They observed that during three sequential trials, the first of the sequence has the greatest increase in oxygenation and blood volume. Later studies examined modeling to extract the evoked response of a single trial from overlapping hemodynamic responses, elicited by stimuli in close temporal proximity in a problem solution task, since in most cognitive studies the stimuli are presented much closer to one another than 10−12 s and before reversal to baseline is achieved.[20]

4. fNIRS Studies in Youth

Chance and colleagues were keenly interested in understanding learning from a neurological viewpoint in the hope of better understanding learning disability and cerebral dysfunction. His fNIRS studies in cognitively normal youth provide a foundation for measuring and interpreting brain activation over the cognitive spectrum that ranges from optimal cognitive function, decline to mild cognitive impairment (MCI) and progression to dementia. It allows researchers to see normal variations in brain function to a given testing paradigm, to learning, attention or non-attention, and longitudinal studies of brain development or training.

4.1. *The dilemma — understanding the response*

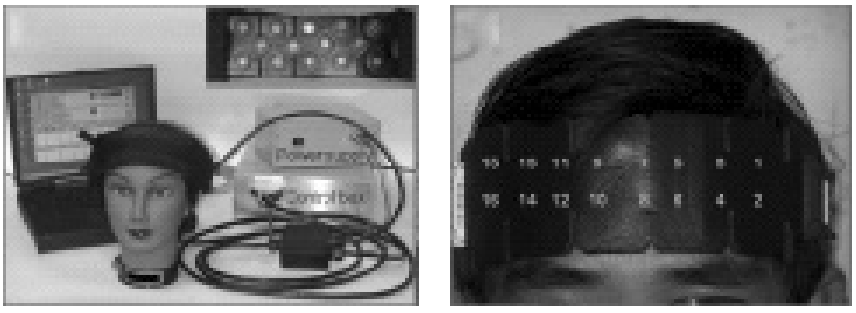
fNIRS studies do not always have a simple, reproducible, and classical activation pattern. The best ways to examine and interpret variance in fNIRS features with neural activation are future challenges required before translation to clinical applications can proceed. Chance *et al.*[10−14] studies showed early on that activation can vary in timing and amplitude across brain regions, cognitive task paradigms, and even within subjects in cognitively intact individuals. Depending on the region being tested, it is affected by left or right handedness, primary spoken language, and sex. The challenges when utilizing fNIRS features to determine pathology or biomarkers for dementia are even greater, due to the effects of physiological aging, medications, frailty, and other illnesses. The following studies by Chance

and colleagues show one approach to testing and managing the unknown.

Britton Chance was dedicated to his summer science program for minority high school students. He applied his CWS-brain imagers, which he called "Cognometers" as a novel, creative, and interactive tool, for youth to experience science. Language and memory were known to be processed in and around the PFC which is easily accessible, non-invasively with fNIRS applied to the forehead. Solving anagrams were utilized to test both verbal memory and learning. An anagram is a scrambled word requiring the subject to rearrange the letters to identify meaningful words. The difficulty level of the anagram increases with greater number of anagram letters. They used a wearable, ear-to-ear detector/sensor array producing 16 channels or "images" from the forehead PFC every second during the anagram solving (see Fig. 1). Data from multiple summers increased the subject number and confidence in results. In one protocol, anagrams were presented in a sequence of three-, four-, five-letter anagrams up to the maximal level of difficulty (few successful solutions) and back to the starting point. Each anagram was displayed for approximately one minute. Students ($n = 7$) did multiple tests each day, 5 days/week, over 6 weeks.

Histograms of several hundred tests per individual in the three-week "training" interval and in the three-week "post-training" interval were plotted. The histogram displayed (a) the most fruitful channels (oxygenation signal), (b) the approximate of the total tests that appeared in those channels, and (c) the maximum signal level observed (micromolar hemoglobin). This study found: (a) that the training effect was very large, pre-training exhibited a chaotic channel distribution for all difficulty levels while trained students gave a higher output and activated only one or two of the 16 channels. The authors concluded, if the tests were too easy (many successful solutions), too hard (few successful solutions), i.e., an ability/difficulty mismatch, frustration, or loss of attention gave similar chaotic patterns; (b) a match between difficulty and ability activated only one or two channels in similar locations for the group. In general, subjects displayed greater oxygenation and needed more time to solve the anagram as the difficulty increased. The study found recognizable changes in patterns after three weeks of learning, and inter-individual differences as well.[18,19]

The approach to examine widely varying activation patterns, "chaos" was that no assumptions on the exact spatial patterns of oxygenations were made. All locations on the PFC were examined, allowed for variations across data sets within an individual for a given brain region, or across individuals for a given region, or across regions. The testing paradigm was repeated hundreds of times and statistical analysis was used to determine significance of the outcome compared to infrequent variation and motion artifacts. See Fig. 2 for representative histogram using fNIRS phase-shift apparatus. The study focused on increased oxygenation with a task, it did not discuss possible alternate patterns during problem solving, namely



(a) (b)

Fig. 1. (a) NIRS Continuous-Wave Imager system. Four light-emitting diodes are centered between 10 detector photodiodes. Light reflected from the brain is converted into digital signals. The digital data is sent to a laptop computer for real-time display and storage. (b) The Imager probe placed on the forehead. The probe covers an area from ear to ear in the horizontal direction and from hairline to eyebrow in the vertical direction. The locations of 16 channels are indicated by numbers. (Reproduced with copyright permission).[17]

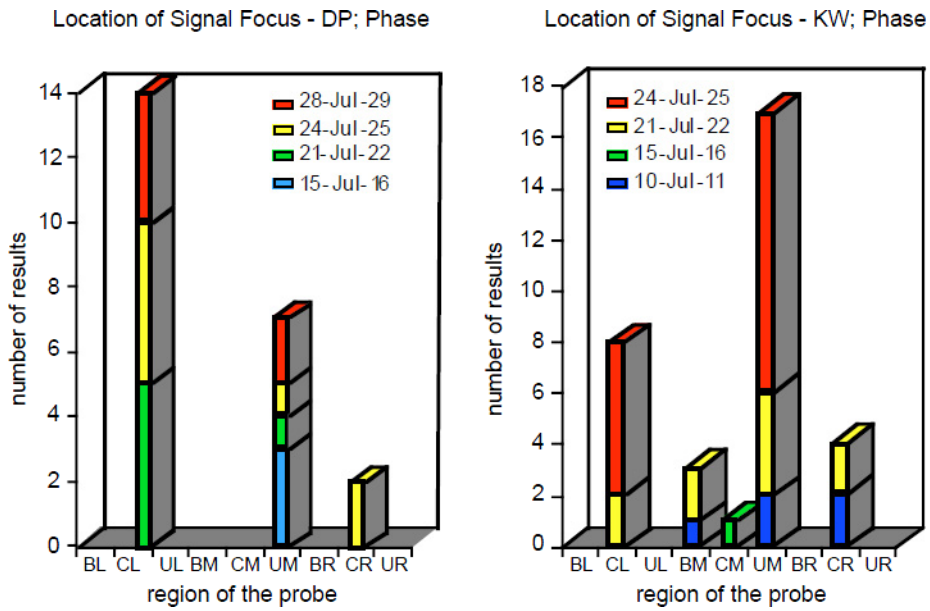


Fig. 2. Histogram display of the position on the forehead of response greater than 20° for backward spelling in 25 and 33 studies of 2 individuals, one a high school junior (left) and the other a college graduate (right). The forehead is divided into 9 squares (each 2×2 cm), centered at the nose bridge, center middle (CM) and extending +4.5 cm from there and 4 cm above the frontal sinuses. The colors refer to the four test intervals over ~20 days. The positions are abbreviated as shown: BL = bottom left, CL = center left, UL = upper left, BM = bottom middle, upper middle (UM), bottom right (BR), center right (CR), upper right (UR). (Reprinted with copyright permission).[11]

deoxygenation during a task other than to report it occurred much less frequently, 17% (32/198) in a study of 6 students performing backward spelling.[11] Later studies do discuss this, particularly with hemodynamic responses shorter than 4 s, seen with an easy anagram level (as compared with medium or hard in the same subjects).[20] Variations from the typical oxygenation response to a task are now well documented and contribute to the complexity and challenges of fNIRS. The physiological meaning of this is unclear. There may be particulars in the protocol design affecting the resulting patterns and responses. Deoxygenation can be the net result from the use of oxygen in the presence of inadequate rCBV, which increases in the focal area from short or insufficient activation. The authors have suggested neural deactivation or inhibition called negative BOLD, which has been reported in fMRI studies as well.[21] Further cross-validation studies between BOLD fMRI signal changes and fNIRS may help elucidate the relationship between these different physiological responses.

For future studies, this research demonstrated that caution must be used when examining fNIRS spatial patterns in longitudinal studies using standardized tests, as repetition alone may have an effect on subsequent regions of activation, whether from learning how to better solve the problem or learning the solutions to the test. On a positive note, it shows fNIRS can provide a physiological measure of the ability to learn, utilize, and possibly rehabilitate a brain region through training. Development of dedicated statistical data processing is necessary to handle the large volume of data and enable large subject studies.

5. Studies in Healthy Aged

In the same timeframe Britton Chance was studying youth, others were utilizing fNIRS in aged subjects. PET and fMRI studies show age-related alterations in neuronal activity patterns.[22,23] In agreement, fNIRS studies show that aging alone can affect cerebral blood oxygenation (CBO) and activation patterns during mental tasks. It is distinguishable by middle age, even in the highly educated. For example, changes measured in the left PFC in cognitively normal young ($n = 13; 28.8 \pm 4.4$ years) and older ($n = 13; 50.7 \pm 8.0$ years) (all right-handed physicians or nurses at a hospital) to verbal fluency test (VFT) and reading found older subjects were

less likely than younger subjects to have a typical pattern of increases in [HbO_2] and rCBV, and older subjects had a greater frequency of decreases in [HbO_2] and rCBV. The authors conclude that functional reorganization and/or alteration of CBO responses may occur during aging.[24]

Kwee and Nakada (2003) utilized fNIRS while testing working memory in 60 "cognitively normal adults," ages 20−90 years; 8 females, 52 males. They administered six cognitive tasks requiring oral language, previously shown by fMRI to activate (to varying degrees) the PFC. They found three (WAIS III)[25] performance subtests: picture completion (missing object), matrix reasoning (which symbol comes next), and picture arrangement (story board) gave a significant ($p < 0.05$) decline in regional oxygen saturation in the DLPF activation as a function of advancing age. On an individual basis, fNIRS quantitative measurements of blood saturation changes did not necessarily correspond to functionality (test scores). The subjects were cognitively normal adults, so it appears the alteration in regional oxygen saturation was not enough to impact cognitive functionality, that there is an "acceptable" decline due to a normal physiological aging process, which must be separated from pathological mechanisms.[26]

It is well established that aging reduces the heart rate sympathetic response.[27] Heart rate and heart or blood pressure medications may also affect CBO. The aged are more likely to be on medications that may confound results if not carefully controlled for, therefore these variables are important to include in fNIRS studies, but are rarely measured. A 2010 fNIRS study evaluated the effect of aging and heart rate on the PFC activity.[28] It measured the mental arithmetic task-induced [HbO_2] changes in the bilateral PFC in young and older females. Increases in [HbO_2] in the right PFC correlated with heart rate, indicating the right PFC activity predominantly modulates sympathetic effects during the task in both groups. The changes of [HbO_2] and heart rate during the tasks in older subjects were significantly smaller than those in younger subjects. These results agree with the above studies and indicate that normal aging affects evoked rCBO response patterns of the PFC during a mental task.[28] Like Chance, they selected the subjects who exhibited an increase in [HbO_2] with a decrease in [Hb] during the task only.

In summary, fNIRS provides a window into sympathetic control, which could be very useful to study the effect of heart rate and blood pressure in CBO, independent of dementia. Distinguishing physiological changes of normal aging from pathological changes such as ischemic vascular disease, which blunts the potential for increased oxygen delivery and results in hypo-perfusion, a possible risk for the development of cognitive impairment, and dementia, is a challenge for the future. It also stresses the importance of closely age-matched control subjects in these types of studies to match normal physiological aging.

6. Studies of Cognitive Impairment and Dementia

While past studies have shown one must use caution when using the exact features of the hemodynamic responses such as maximal amplitude of oxygenation during activation and/or response time to peak, to quantify cognitive state of the subjects, some studies show they are key features distinguishable between groups of cognitively normal, Mild Cognitive Impairment (MCI), and probable Alzheimer's Disease (AD).

An excellent study utilizing a whole-head fNIRS system, 32 controls (healthy, medication free, right handed), 15 MCI and 15 AD, equal male and female, mean age 69 years, were asked to pronounce as many nouns as possible beginning w/a′, ka′, and ta′, consecutively with 15 s for each letter. The three groups were matched in terms of age, sex ratio, and education. Only positive [HbO_2] changes during the tasks were utilized due to limitations of the analysis system used. Results of cortical [HbO_2] and hemodynamic waveform in the frontal and parietal cortex showed the amplitude of oxygenation increases were significantly lower in the frontal ($p = 0.00037$), and the bilateral parietal cortex (left; $p = 0.14$, right; $p = 0.000066$) areas in the AD group. The MCI group also had significantly lower oxygenation increases but only in the right parietal area ($p = 0.0012$). They report the sensitivity for the activation amplitude to be 71% for AD and 40% for MCI, with a specificity of 94%, comparable to those of others they reference.[29]

Herrmann *et al.* (2008) investigated 16 patients with AD and 16 healthy subjects (similar in age and sex) during performance of a VFT.[30] Their results

also showed the classical activation pattern during active phase as compared to baseline phase, decreases in [Hb] and increases in [HbO_2], and with a reduced increase of [HbO_2] for AD patients. Their results indicate a diminished activation of the dorsolateral prefrontal cortex (DLPFC) in patients with AD, particularly the LEFT hemisphere, but in contrast to the above study, showed non-laterality in AD. They also found a reduced response in persons on hypertension medications. Future research must investigate decreased activation patterns and non-laterality and tease out the confounding variables to show whether this might be a suitable biomarker and predictor for MCI and AD. It is important to note that while the parietal and DLPFC regions differ anatomically, they can have overlapping functions and connections, and that spatial resolution is a limitation with fNIRS. The above studies are a sample of the potential and challenges of applying fNIRS to the clinical assessment of biomarkers for cognitive impairment and dementia.

7. Measuring Treatment for Impaired Cognitive Function and Dementia

Since there is no cure for dementia, there is urgency for better screening tests and early identification of cognitive impairment so that treatment can begin before irreversible damage is done. Medications such as galantamine and donepazil are routinely used for AD to treat the cholinergic deficiency at the synaptic junction. The efficacy of these medications, thought to slow the course of the dementing process, is difficult to measure with neuropsychological tests alone. This is because of the day-to-day variability of cognitive function, which is further confounded by variables such as chronic illness, medications, sleep, fatigue, and mood. Recent studies[31,32] have shown the addition of technology such as fNIRS may assist in the assessment of pharmacological treatments by measuring the physiological change, i.e., the neurocoupling or rCBV improvements brought about by the medications.

Epidemiological studies show diabetes, hypercholesterolemia, hyperhomocysteinemia, and hypertension are associated with development of vascular dementia (VaD) and AD and are supported by histopathological and functional changes in small and large vessels. Despite the fact AD has been predominantly associated with amyloid and neurofibrillary tangles, with forebrain cholinergic deficits, and neuronal loss in the cortex and hippocampus, a neurovascular hypothesis for the pathogenesis of AD suggests pathogenic cascades, including dysregulation of cerebral blood flow, hypoperfusion, faulty clearance of amyloid-B peptides, and abnormal angiogenesis.[33]

The ability of NIRS to measure vascular reactivity, hypoperfusion, and ischemia may provide a more direct and faster approach to the clinical application of NIRS. It may enable clinician scientists to measure the effectiveness of medications such as acetyl cholinesterase inhibitors, aimed to alter neuroreceptors and cerebral blood flow.

In 2007, Bar *et al.* utilized co-registration of transcranial Doppler and NIRS to assess CO_2-induced vasomotor reactivity (VMR) (vasodilation) in young ($n = 20; 24.9 \pm 2.3$ years) and older ($n = 20; 64.7 \pm 10$ years) controls and patients with VaD ($n = 17; 69.4 \pm 10.0$ years) and AD ($n = 20$; 66.9 ± 11.9 years) before and after 8 weeks galantamine treatment, an acetyl cholinesterase inhibitor. Subjects were determined free of carotid artery disease by transcranial Doppler (TCD) and grouped by diagnostic and clinical exams including cranial MRI, cerebrospinal fluid for tau protein, MMSE, and Wechsler Memory test. Cerebral blood flow velocity was measured by TCD at the temporal bone window; changes in rCBV, [HbO_2] and [Hb] were measured by NIRS in the left middle PFC.[31]

TCD revealed significantly reduced VMR (% change in CBF velocity and total mmHg) in both AD ($p = 0.01$) and VaD ($p < 0.03$) compared to old controls but no significant differences between AD and VaD groups, nor significant differences between normal young and normal older subjects. Galantamine treatment showed significant increases in VMR in both AD and VaD.

NIRS showed significantly reduced [HbO_2] in VaD compared to old controls ($p < 0.006$) and young controls ($p < 0.0001$). Reduced [HbO_2] in AD differed significantly only from young controls. Galantamine treatment showed significant improvements in [HbO_2] in VaD only ($p < 0.01$), but increased variation trending higher in AD. This is in agreement with another study that measured brain [HbO_2] after treatment with galantamine in mild to moderate AD patient group and found no clear treatment effects measured at four and eight

weeks.[32] These important differences need to be explored. Of note, galantamine is not expected to improve AD symptoms, but prevent decline over time. While the exact time for full physiological effect is not known, more than four and eight weeks are required to measure decline in function. In clinical practice, neuropsychological tests do not attempt to measure decline in function earlier than six months.

Clearly these two complementary technologies offer increased information about mechanisms in small and large cerebral vessels and attenuation by treatments. The information could potentially be a suitable predictor of the effectiveness of treatment for AD and VaD.

8. Unique Challenges in Dementia Research

A major challenge in dementia research is the specificity of neuropsychological tests to diagnose AD and distinguish the difference between mild, moderate, and severe dementia groups. The AD diagnosis is commonly over-utilized and generalized to mean a cognitive impairment or dementia similar to that seen in AD but may not have been verified by pathology. Most AD is marked by plaques, neurofibrillary tangles, or tau protein in cerebrospinal fluid. These biomarkers are rarely examined in patients, especially in earlier studies before the technology to do so became available. Vascular dementia can also produce a pseudo-AD and is estimated to cause 30% of dementia. Studies discussed earlier showed VaD and AD can have marked different responses. Some studies allowed subjects with depression, common with dementia, but which is shown to have a variable activation pattern, with primarily frontal cortex hypoperfusion.[34] Although expensive, currently MRI and other diagnostic tests must be co-utilized to more accurately diagnose pathology associated with a particular dementia and properly separate groups. Correlation of NIRS/fNIRS with the clinical pathology and behavioral attributes will provide more information of interest to clinicians. If it has application to patient care and management, it will increase the value of NIRS and fNIRS in their clinical practice. Perhaps in the future, NIRS/fNIRS biomarkers, together with the clinical phenotype, can predict the underlying neuropathology providing better utilization of this cost-effective technology.

The advanced aged (older than 80 years), frail, and more impaired subjects are particularly challenging to study as they are often unable to undergo lengthy, repetitious studies. PET, SPECT, and fMRI are unsuitable for persons with fear of small spaces, or if unable to lie still for prolonged periods due to discomfort and pain from past injuries or arthritis. The stimulation and confusion of the hospital environments can be too much for some elderly patients. fNIRS has a distinct advantage over PET, SPECT, and fMRI in that it allows subjects to be seated comfortably in a lounge chair, with the ability to have short sequential testing sessions with time to rest and move around, in any quiet, even familiar environment available. Despite the technology used, these aged subjects may have difficulty staying still, staying awake, and understanding instructions (based on author's clinical experience). Protocols will need to be short but appropriate and probes must be comfortable and resistant to motion artifacts.

8.1. *Ethical issues — the ability to provide consent*

While informed consent from the research subject is possible when they are competent to give it, many persons with dementia are no longer able to provide consent by the time they are diagnosed and could potentially be entered into a research program. Rather than deny these persons access to new treatments that are being studied, researchers usually proceed by surrogate consent, i.e., another person, generally the primary caregiver, consents on behalf of the subject. Institutional committees for human subject research generally permit that for minimal risk research such as fNIRS/NIRS, in the absence of an advance directive, surrogate consent is acceptable, and all individuals should be allowed to enroll, even if there is no potential benefit to the individual. However, the study of demented elders is still controversial and researchers may find increased resistance to studies in this vulnerable and protected population.

While recognizing the importance of studies including all willing volunteer subjects with dementia, the goal is early detection of risk factors to prevent cognitive impairment, or monitoring treatment of cognitive impairment to prevent progression to dementia. That population is younger,

more likely to be physically and functionally normal, and less likely to be cognitively impaired. They are more able to understand consent forms, follow instructions, and come to repeat testing sessions. The aging population (older than 55 years) has a vested interest in preventing and treating dementia, and they are likely to be willing participants when treated with respect and understanding.

8.2. *Spatial specificity*

The exact areas activated in fNIRS studies can be difficult to determine. For example, definitions of PFC, dorsolateral PFC, and anterior PFC are variable. The PFC, being the anterior part of the frontal lobe of the brain, lying in front of the motor and premotor areas, encompasses a large area, including parts of Brodmann areas 8−11, 44−47. Dorsolateral PFC is roughly equivalent to Brodmann areas 9 and 46, but by broader definitions could include Brodmann areas 9−12 and areas of 45, 46 (see Fig. 3).[35] Identification of probe location by international 10−20 EEG[36] and in relation to Brodmann areas could improve spatial specificity, ease and confidence in comparison between studies.

9. Challenges and Future Opportunities

The previous studies are a sampling to demonstrate how far NIRS has come in the relatively short time since Chance and other researchers did their foundational studies. Despite this abundance of valuable research, NIRS and fNIRS are still relatively unknown and unavailable to clinicians.

There are several good review articles discussing strengths and weaknesses of fNIRS,[37] cross-validation between fMRI and fNIRS,[38] and suggestions for future directions of fNIRS research.[39] In brief, problems with skin-probe coupling, path-length variability, quantitation, whole head imaging, motion artifacts, variability and interpretation of results, purity of test groups, correct paradigms and protocol designs, etc. must be solved. These challenges are not insurmountable given the international NIRS/fNIRS optical imaging community. They have made monumental theoretical and technological advances in optical imaging in a relatively short time. Better probe designs, standardized and validated testing paradigms, with increased accessibility to NIRS/fNIRS, including improved data management and statistical analysis, are needed to establish NIRS/fNIRS as a complimentary neuroimaging technology. Larger studies, improving repeatability and reporting sensitivity and specificity for this new application are needed.

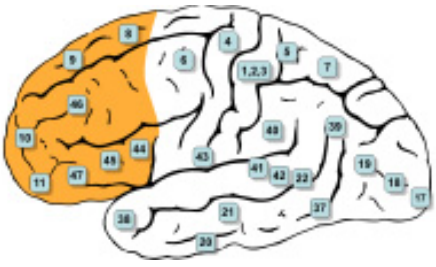


Fig. 3. Brodmann's areas — The PFC, being the anterior part of the frontal lobe of the brain, lying in front of the motor and premotor areas, encompasses a large area, including parts of Brodmann's areas 8−11, 44−47.

We do not yet understand the exact mechanisms and meaning of the fNIRS patterns, but if we can describe the underlying biochemistry, we gain an understanding of neurologic function and dysfunction. We are then able to reliably identify abnormal cerebral circulation patterns and responses and subsequently follow progression or interventions in a longitudinal manner. fNIRS provides an excellent tool to study a major underlying cause of cognitive decline and cerebral micro-vascular disease and possibly identify those at risk for progression to dementia. It could provide a much-needed tool to clinicians, who aim to prevent cognitive decline by identifying those most at risk and guide timely and appropriate interventions.

There is now considerable research evidence to suggest that NIRS cerebral vascular reactivity and fNIRS activation patterns could be a sensitive, cost-effective means of screening for early biomarkers of pathology and a predictor of risk for cognitive impairment or progression to dementia. Its portability and suitability for all subjects, including the frail and aged, removes many barriers for frequent and early testing compared to PET, SPECT, and fMRI. The early identification or diagnosis allows a person to plan for the future, allow medications that may slow diseases progression, and delay functional dependency and nursing home placement.

It is time for large, longitudinal, prospective studies utilizing NIRS and fNIRS in persons older than 50 years to determine predictive sensitivity and specificity. The "potential" value of this

technology for cerebral monitoring of tissue oxygen sufficiency and diagnosis and treatment of dementia must be realized. The aging of society and increasing incidence of dementia presents a compelling need. The international NIR optical imaging community must continue to build upon the legacy of Britton Chance. *For those who are aging, the clock is ticking.*

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