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NIRSIT: Clinical Testing of Near Infrared Spectroscopy (NIRS) for Quantitative Assessment of Depression

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STUDY PROTOCOL

NIRSIT: Clinical Testing of Near Infrared Spectroscopy (NIRS) for Quantitative Assessment of Depression

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Lay Summary:
We will assess whether a wearable and portable device that detects changes in blood flow in the frontal lobe in the brain is able to detect subtle changes in the symptoms and severity of depression. We will correlate changes in blood flow monitored at 96 locations to symptoms and the severity of depression as measured by validated survey instruments. We will develop a robust testing regimen that improves the sensitivity and specificity of current depression diagnostic tools.

Project Summary:
We will assess intra-individual variability in the amount of activity elicited in the prefrontal cortex by emotional stimuli comparing patients being treated for major depressive disorder to normal controls. Prefrontal activity will be measured using a non-invasive, wireless, portable device that is approved in Korea to distinguish various psychological disorders. The device, called NIRSIT, produced by a Korean company OBE Lab, uses near infrared light to measure changes in the amount of hemoglobin delivered to various portions of the brain. This study differs from previous studies done in Japan in that standardized pictures, selected to elicit an emotional response will be used as stimuli, and latency of response will be added with the hopes of improving the diagnostic specificity of the device. The timing of frontal lobe saturation changes will be correlated to the timing of the picture. NIRST readouts will include lag time, localization, and laterality of response.

Specific Aim:
Develop a NIRSIT testing protocol that can be administered in the diagnostic setting and reliably distinguishes the symptoms and severity of depression.

Hypothesis:
1. Non-depressed patients will have greater variations in frontal lobe blood flow while performing the verbal fluency and cartoon humor reaction tasks.
2. The lag time for changes in frontal lobe blood flow response time will vary with severity of depression symptomatology.

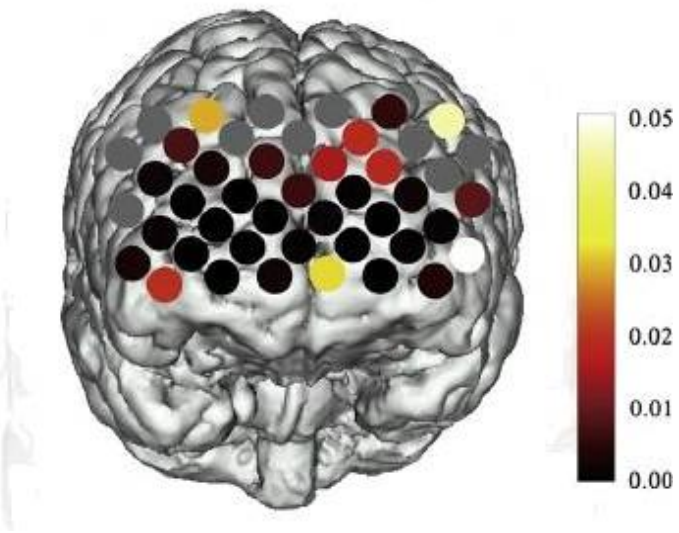
Design:
Repeated measure (up to five visits per subject) comparison of patients being treated for depression with control non-depressed subjects.

Background and Significance:

Background: The history of utilizing the near infrared (NIR) spectrum (650-1000nm) in cognitive studies is chronicled in a recent review[1]. Taking advantage of the fact that human tissue is relatively transparent to NIR and hemoglobin absorbs those wavelengths of light, in 1977, Jobsis developed a non-invasive device able to detect oxygenation changes in the brain. He later used this technique to study cerebral oxygenation in new born infants. The first publications describing NIRS results began to appear in the early 1990s, and in 2000, the first commercially available device was marketed. In 2009, Hitachi released the first battery operated wireless/ wearable device. In the 3 years preceding this 2012 review[1], ~400 articles utilizing this technology have been published in the fields of neurology (Alzheimer's disease, dementia, depression, epilepsy, Parkinson's, rehabilitation, stroke), psychiatry (anxiety, substance abuse, schizophrenia), education (attention, comprehension, reasoning) and basic research (pain, sleep).

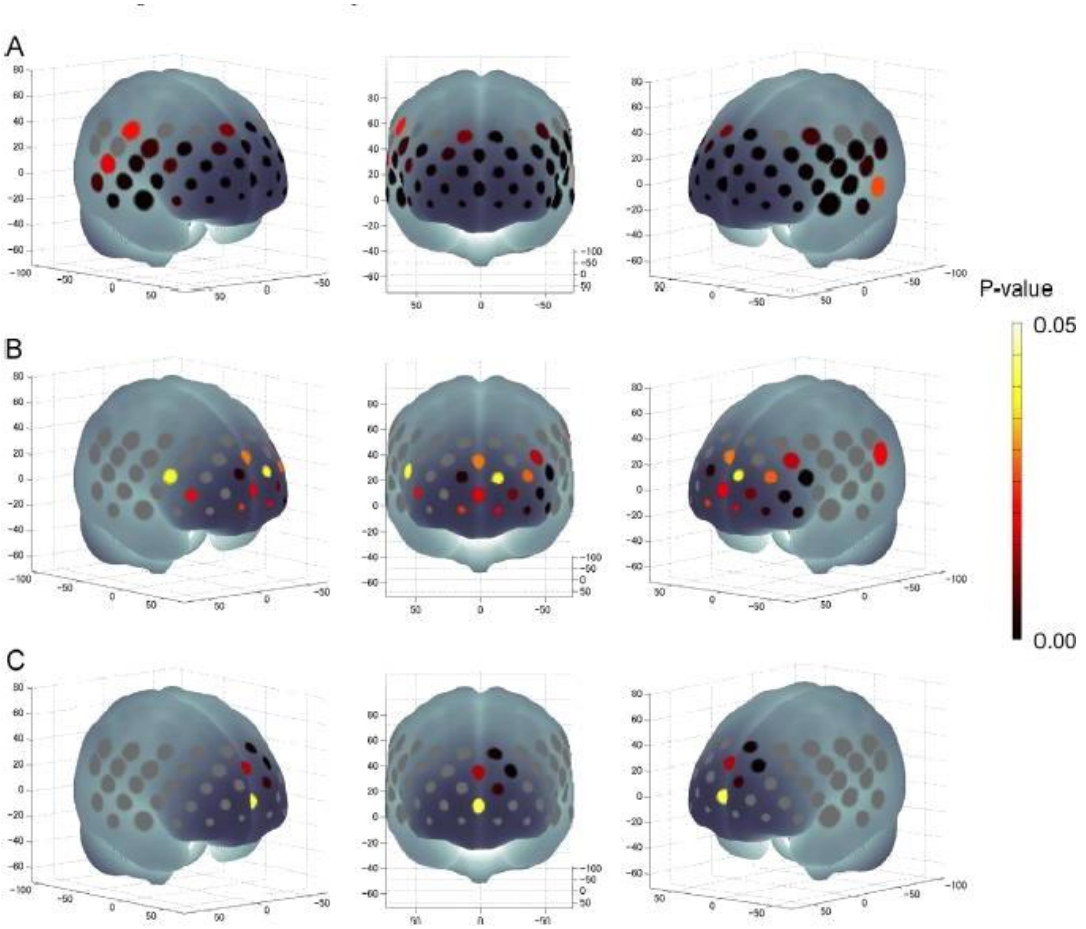
Device: Near Infrared Spectroscopy (NIRS) provides a non-invasive measurement of frontal lobe blood flow and saturation over time. The NIRS device has ninety-six (96) two color infrared lasers and paired photodiodes which record oxygen saturation to a depth of 2 cm from the frontal cortex of humans. NIRS provides a measurement of blood saturation from over 200 prefrontal regions providing high spatial resolution at a scan rate of 32 Hz providing high temporal resolution. The NIRS can provide real-time cognitive studies which can discriminate cognitive workload, concentration, and emotional stress and anxiety. NIRS provides 200 measurements of oxy, deoxy, total hemoglobin, and heart rate 32 times per second

Preliminary studies:



The diagram above illustrates areas of the prefrontal cortex where changes in oxy-, deoxy-, and total hemoglobin, during a verbal fluency test differed in patients with major depressive disorder when compared to normal controls[2]. Areas indicated in grey did not differ. The color corresponding to Bonferroni-corrected p-value of significance is indicated in the heat map scale on the right. Areas indicated in black had the greatest difference. Normal controls differed in thirty-seven channels whereas depressive patients differed in six channels. The verbal fluency task involves having participants list items belonging to semantic categories (vegetables, animals, machines).

Another study showed a similar negative correlation (severely depressed patients had lower NIRS activity) of front and right temporal activation with the severity of depressive symptoms as measured with Hamilton Rating Scale[3]. In 2009, the Japanese Ministry of Health, Labor and Welfare approved NIRS to distinguish between schizophrenia, depression and bipolar disorders.[3] A review summarizes areas of the prefrontal cortex (PFC) where emotional stimuli elicit a NIRS response[4]. Tactile stimulation with velvet elicited a response in the bilateral anterior PFC; an infant's smiling face in the occipital frontal lobe (OFC); arithmetic problem-solving stress stimulated the autonomic nervous system (ANS); and there were pronounced gender differences in response to emotional video clips.



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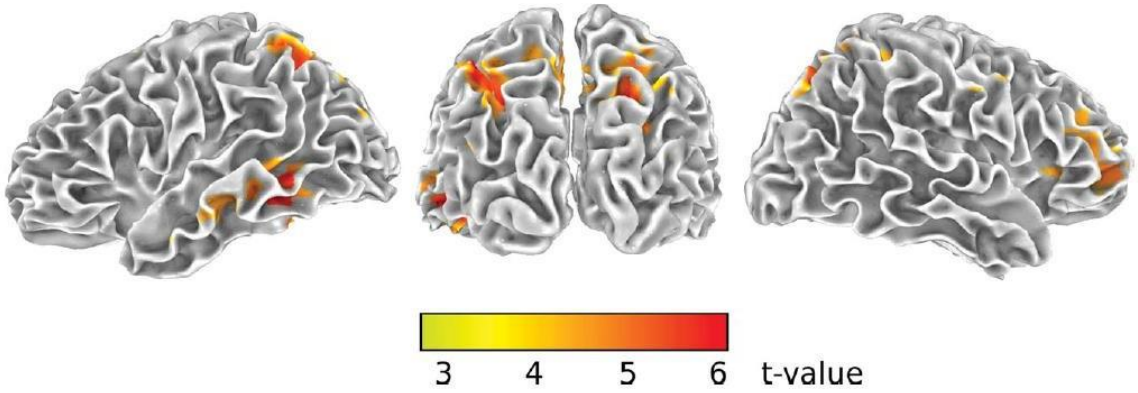
A recent study seems to indicate that NIRS can distinguish different components of depression[5]. The Beck Depression Inventory (BDI) is the most widely used self-rated measure and is focused mainly on depressive cognitions. The Hamilton Depression Rating Scale (HAMD) is the gold standard observer-rated measure which focuses mainly on somatic/vegetative symptoms. The profiles indicated in A above show the areas of significantly different NIRS activity in patients whose BDI and HAMD depressions scores were concordant when compared to normal controls. The profiles in B show that patients with discordant BDI and HAMD depression scores had fewer areas that were significantly different from controls. Profiles in C indicate the areas where patients with discordant scores differed from those with concordant scores. NIRS activity in these areas as well as other adjacent areas seemed to vary with the severity of depression scores[5].

Longitudinal six-month changes in NIRS activity were correlated with the Social Adaptation Self-evaluation Scale (SASS) and inversely correlated with HAMD[6]. This study, where 10 patients with major depressive disorder were subsequently tested 6 months later showed increased NIRS activity was correlated with increases in social functioning. A larger study of 29 patients showed significant increases in NIRS activity and social functioning in patients with depressive disorder when comparing scores prior to the initiation of antidepressant medication treatment when compared to an 8-week follow-up visit.[7]

In this emerging field, variations in experimental design could produce discrepant results [8]. The authors stress the importance of including sufficient experimental conditions, examining

individual as well as group level differences and considering experimental tasks that are relevant to the diagnostic setting.
Much of the previous work in Japan is based on verbal fluency test that would provide limited diagnostic value in the United States.



A task that shows promise as a reliable and reproducible test that could be administered in a diagnostic setting is the Emotional Working Memory Task (EWMT); a series of pictures taken from the International Affective Picture System (IAPS) database and developed by the National Institute of Mental Health and the Center for Emotion and Attention at the University of Florida. The figure above shows areas of the brain where there were significant differences in activity associated with emotional vs neutral images from the IAPS[9].

Another parameter that could be useful for distinguishing depression severity and various dimensions of depression is the lag time between the emotional stimuli and the time a response is elicited[10].

Procedures / Methods:
All subjects will fill in three or four surveys: Hamilton B Depression Rating Scale (HDRS), Beck Depression Index (BDI), Patient Health Questionnaire-9 (PHQ-9) and Mini International Neuropsychiatric interview (MINI). Then, they will undergo NIRSIT testing. During the NIRSIT (Near Infrared Spectroscopy) test, we will strap the device on the subject's forehead, and administer the Verbal Fluency Test (VFT) and the Cartoon Humor Reaction. The Verbal Fluency Test asks subjects to say words beginning with certain given letters. The Cartoon Humor Reaction tasks asks subjects to view pictures with cartoons.

Instruments:
- Hamilton B Depression Rating Scale (HDRS)
- Beck Depression Index (BDI) and
- Patient Health Questionnaire-9 (PHQ-9)
- Mini International Neuropsychiatric interview (MINI)
- Verbal Fluency Test
- Cartoon Humor Reaction

Statistical Methods:
Repeated measures ANOVA as well measures of concordance will be used. Non-parametric linear regression analysis will be attempted between NIRS score and depression inventory score. Three different measures of concordance: 1) sensitivity (comparison of depression symptom severity score to NIRS assessment of neurocognitive responsive time). 2) positive predictive value (PPV) (the proportion of diagnosis correctly identified by NIRS when compared to the depression inventory scale) and 3) Kappa statistic, used to describe the degree of concordance with established grading criteria. $K < 0.20$, poor, $K = 0.20$ to 0.39, fair; $K = 0.40$ to 0.59, moderate; $K = 0.60$ to 0.79, very good; $K > 0.80$, excellent.

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1. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 2012;63:921-35.
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3. Noda T, Yoshida S, Matsuda T, et al. Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: a multi-channel near-infrared spectroscopy study. J Psychiatr Res 2012;46:905-12.
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7. Pu S, Nakagome K, Yamada T, et al. Prefrontal activation predicts social functioning improvement after initial treatment in late-onset depression. J Psychiatr Res 2015;62:62-70.
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9. Keil A, Costa V, Smith JC, et al. Tagging cortical networks in emotion: a topographical analysis. Hum Brain Mapp 2012;33:2920-31.
10. Gallagher P, Nilsson J, Finkelmeyer A, et al. Neurocognitive intra-individual variability in mood disorders: effects on attentional response time distributions. Psychol Med 2015;45:2985-97.

Non-significant risk justification:
No clinical decisions will be made based on the data acquired for this study. The NIRSIT data is collected solely for the study. The NIRSIT data will not be used for any clinical decision making and therefore the study qualifies for NSR.

NIRS has been studied in Japan since 2000[1]. The OBE Lab NIRSIT device has more sensors than the Hitachi ETG-4000, which has US 510K clearance (K042501) since Oct 12, 2004 with an intended use of the measurement of relative levels of cerebral deoxyhemoglobin and oxyhemoglobin, but has a similar safety profile. The OBE Lab NIRSIT device has a higher sensor count (96), higher number of assessed voxels (200), higher temporal resolution (30 Hz), but similar safety profile to the Hitachi ETG-4000. The Hitachi ETG-4000 would be the predicate device for FDA 510K clearance.

Sample size: upto 90

Normal: 30 patients - Control subjects could be patients, staff or public members who self-indicate that they are not severely depressed.

Depression: 60 patients with Major Depressive Disorder

Depressed patients will include those whose initial depressive symptoms were sufficiently severe such that they and their treating physician have decided that they may benefit from treatments such as electroconvulsive therapy (ECT) or ketamine infusion.

Sample size justification:
Meta-analysis of NIRS studies for depression demonstrate similar response magnitude and all studies with more than 20 patients in each group demonstrated a significance between depressed and healthy controls without using repeated measures. Repeated measures analysis with the patient as their own control over time could provide sufficient power to correlate symptoms and severity of depression to NIRSIT readouts. Varying the type of emotional stimuli and comparing lag times will provide additional parameters on which to increase the specificity of diagnosis.

Inclusion Criteria:
1. All patients will sign informed consent.
2. Normal: patients 18-65 years old with no evidence of neurocognitive dysfunction or depression.
3. Depressed: Patients with a diagnosis of Major Depressive Disorder.

Exclusion Criteria:
We will exclude subjects to do not sign an informed consent.

Exclusion of control patients:
1. Depression
2. Other major psychiatric disorders

Exclusion of Depressed patients:
1. Mixed diagnosis or unclear diagnosis of depression
2. Not receiving therapy for depression

Determination of eligibility:
Control subjects will be healthy people, who do not have depression or other neurologic problems willing to volunteer to be in the study. They will be approached for consent. If they consent they will be included in the NIRSIT study.

Patients with major depression scheduled for ECT or Ketamine infusion will be reviewed for eligibility. If patients meet inclusion criteria they will be approached by psychiatric staff to see if they are willing to participate in the study.

How is contact initiated?
Flyers will be posted outside the Anesthesia Business Office, at the San Francisco VA Medical Center to provide information about the study and how to enroll.

Psychiatry attending physicians will identify and approach depressed patients to ask if they would like to enroll in the NIRSIT study.

Health Information:
No information from control patients will be obtained from the medical record.

Depressed patients will be identified as part of their normal clinical care for major depressive disorder. Their clinical history will be available for the study physician prior to consent as part of their routine care for their major depressive disorder.

Research related Risks:
- Loss of privacy. All clinical studies have some risk for loss of privacy. Medical and psychiatric records are reviewed by study staff and recorded for research purposes. All records will be stored as encrypted files or in locked storage to reduce risks.
- NIRSIT device uses infrared light. The FDA has concluded that the light emitted by the device is harmless and poses non-significant risk.

Minimizing risks:
1. All study records are stored in locked file cabinets in locked offices. The risk of loss of study related materials is small.
2. NIRSIT and depression inventory testing will be done in a manner that is sensitive to patient needs and minimizes possible embarrassment.

Resources:
- NIRSIT and depression inventory testing will be performed by research staff.
- In-patient psychiatric facilities are available when needed at the SF VAMC for patient with major depressive disorder. Psychiatric evaluation and treatment is available 24/7/365 for all patients at the SF VAMC.

Benefits:
The NIRSIT test may improve the ability to distinguish diagnostic symptoms of depression and thereby make possible more specific treatments and therapy improve the care of future patients with depression.

Risk-to-benefit ratio:
NIRSIT and depression inventory testing pose no more than minimal risk to subjects. This study may show that the device and testing protocol are able to improve the sensitivity and specificity of depression diagnostics and thereby make possible more specific treatments and therapy improve the care of future patients with depression.

Data and safety monitoring plan:
The PI will report to the IRB any incident where the monitoring device may have caused harm to participants.

Extra Confidentiality Measures:
All standard approaches to the confidentiality of clinical care will be utilized.
Control subjects who are not VA patients, will only have research case report forms. Control subjects, who are not VA patients, will not get a VA medical record.

The NIRSIT device uses facial photography (frontal and profile images) to assess and record spatial registration of the NIRSIT device with the eyes, nose, and ear. This registration is used to ensure that frontal lobe volume elements (voxels) are reproducible over time. These images will be stored on research computers for analysis of NIRSIT device spatial registration. No facial images will be published.

Subject Payment Schedule:
All study participants you will be paid up to $100 for taking part in this study; $20 for each NIRSIT session.

1. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 2012;63:921-35.
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