Coordinated, Multimodal Neuromodulation and Neuroimaging

PCNC (PSYCHOLOGY CLINICAL NEUROSCIENCE CENTER) AND MRN (MIND RESEARCH NETWORK)

I. CONTEXT

This profile spans two research centers. Dr. Vincent P. Clark is the founding Director of the Psychology Clinical Neuroscience Center (PCNC), which is located within the Department of Psychology at the University of New Mexico. The mission of the PCNC is the development of new knowledge regarding how normal and abnormal behavior and cognition arise from the brain.

Dr. Clark was formerly Scientific Director of the MIND Research Network (MRN), which is located on UNM's campus, and is a non-profit organization that is a member of the Lovelace Family of companies. It offers a combination of methods for neuroimaging, and focuses on a combination of imaging, data analysis and bioinformatics for clinical and cognitive neuroscience research.

II. DESCRIPTION

Faculty associated with the PCNC and MRN have a long history of performing structural and functional imaging studies of the human nervous system, using a variety of neuroimaging modalities, including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) and others. Each method offers a variety of advantages and disadvantages for a particular neuroscience question, depending on their spatial and temporal resolution, relative cost and signal contrast to noise at the individual and group levels. By combining imaging methods, additional information is gained, and can be useful to confirm findings across modalities.

A. Applications of Neuroimaging

These neuroimaging methods have been applied to a variety of questions. Our work has included both the brain basis of healthy human cognition, primarily perception, attention and memory, as well as differences in brain organization associated with psychiatric illnesses such as addiction and schizophrenia, and neurological disorders such as traumatic brain injury, stroke and Huntington's disease, among others. We have found that imaging can predict relapse in recovery from stimulant addiction with up to 80% accuracy [1] (Figure 1). Through the efforts of our laboratories and others, neuroimaging has made great strides in understanding the brain basis of healthy cognition as well as neurological and psychiatric illness.

Non-invasive brain stimulation combined with neuroimaging has the potential to revolutionize cognitive enhancement and provide more effective treatments for brain and mental illness

Figure 1. Brain regions whose reduced magnitude of activity predicts relapse in recovering stimulant addicts using fMRI, from [1].

B. Limitations of Neuroimaging

While there has been tremendous impact of neuroimaging in gaining a better understanding of the brain basis of cognition and illness in academic circles, the impact of this work on real-world problems and goals has been limited. One is that neuroimaging is mostly observational, providing correlations between clinical or behavioral variables and brain states. As with any correlation, these methods are unable to test causation directly, which must be verified using other means. In addition, while neuroimaging has been successful in the diagnosis of neurological illness, and to a lesser extent psychiatric illnesses, it has been a failure both in terms of reducing the impact of neurological and mental illness on human health. This is shown in part by the increasing relative rank order of major brain and mental illnesses compared with other forms of illness [2]. Within the disability-adjusted life-year loss ranks for the top 30 diseases and injuries in the US from 1990 and 2010, the most prevalent brain and mental illnesses (ranked from more to less impact of lost life-years in 2010: major depression, drug use disorders, Alzheimer's disease, anxiety disorders, alcohol use disorder and schizophrenia) have moved up in their relative ranking on the average, while physical ailments like road injury and HIV/AIDS have reduced greatly over the same period. This suggests that treatments for brain and mental illness have not improved as quickly as other forms of medicine over the past decades.

Without effective methods of treatment for these disorders, more accurate diagnoses obtained from neuroimaging do not provide substantial benefits. In order to apply information derived from neuroimaging and take full advantage of its anatomical and temporal characterizations of brain function, new methods of treatment must be developed in order to use this information to its fullest possible benefit. Being able to normalize brain function, that is, to guide disordered and pathological brain function to a healthier state, may be one key to reducing the impact of or curing brain and mental illness.

C. Non-invasive Brain Stimulation (NIBS)

Over a decade ago, our laboratory began experimenting with NIBS in conjunction with neuroimaging. All techniques for NIBS apply some form of energy to the nervous system, including electromagnetism (electricity, magnetism and light) and physical pressure (ultrasound and others) in order to influence its activity, and thus to influence behaviour. This includes short-term changes during treatment, and longer term effects related to neuroplasticity. Because NIBS can be applied to targeted anatomical locations with a specific temporal profile, it can be used to influence neural activity supporting particular behaviours or symptoms. Also, when used within pre-defined limits of energy deposition, it is found to be safe, in part because of its anatomical focus that reduces effects on other body organs.

While NIBS offers hope for improved methods of treatment, it has been plagued by a number of failed replications [3] and uncertainty regarding its mechanisms of action, or indeed if any real changes in brain function other than placebo effects occur under certain situations. In these cases, neuroimaging may provide a benefit to NIBS, by documenting changes in brain function associated with its application, and by using neuroimaging to guide the application of NIBS to achieve a specific change in brain function with greater efficacy and reliability. The following describes some methods of NIBS used in our laboratory, and efforts in our laboratory to combine NIBS with neuroimaging to optimize and characterize the effects of NIBS.

1) Transcranial Electrical Stimulation (tES)

Electrical brain stimulation takes many forms. The minimum requirements are a controlled current with at least two electrodes closing a circuit across the scalp. Dosages for transcranial direct current stimulation (tDCS) are typically 1-2 mA for 10-30 minutes, although higher current or longer durations and have been used [4]. The number of tDCS protocols that can be reasonably conceived of, including differences in electrodes (size, number and locations) and applied current (polarity, amplitude and duration), results in over 4 million possible combinations. In addition, if methods of current modulation are considered, such as transcranial alternating current stimulation (tACS) where current is modulated in a sine wave fashion, or random noise, pulsed, sawtooth or many other time varying patterns, and also their additive combination, then a nearly infinite variety of protocols are possible. Each protocol may augment or interfere with anatomically distinct sets of neurons operating with different temporal profiles through resonant mechanisms that have been only partially explicated so far, and therefore may have a large variety of different effects.

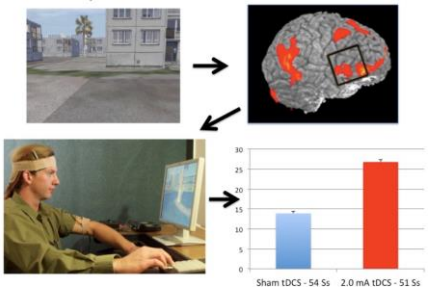

Figure 2. Shows procedures used in [5] to develop a tDCS protocol able to increase learning by a factor of 2. Upper left, an example target detection training stimulus. Upper right, brain regions found using fMRI involved in learning to detect targets. Lower left, application of tDCS during training, positioned over regions indicated. Lower right, effect of verum tDCS (red) vs. sham control (blue) on performance improvement with training.

Our initial studies used a tDCS protocol planned using anatomical data derived from fMRI and MEG studies [5]. Subjects learned to detect targets hidden in complex pictures taken from a virtual training environment. This tDCS protocol approximately doubled learning rate and d', a measure of signal detection, and is one of the largest reported effects of any treatment on learning thus far. This line of research has been replicated in multiple subsequent studies, both in our laboratory at UNM [6] and independently at another university [7]. We have also identified some cognitive [8] and neural mechanisms of this tDCS protocol using fMRI and magnetic resonance spectroscopy [9] and other imaging methods, and are finding inc current studies that other forms of learning are also accelerated using this tDCS protocol.

With our partners at HRL Laboratories, LLC, we have developed a novel method of closed-loop alternating current stimulation (CL-tACS) patterned using EEG recorded during sleep. CL-tACS stimulation was configured to have the same frequency and phase as participants' endogenous slow wave oscillations (0.5 to 1.2 Hz) derived from EEG recorded as they slept. CL-tACS was applied for 5 full cycles at their endogenous frequency and phase over bilateral frontal electrodes (F3 and F4) at 1.5 mA per hemisphere with temporal/mastoid return electrodes. Using this, we found evidence for increased memory consolidation during sleep [10] using the same target learning task used in [5], with a peak effect occurring with about 220 stimulation events [11], and with additional beneficial effects on sleep quality and efficiency [12].

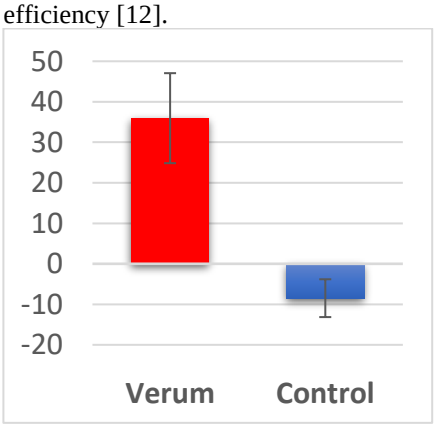

Figure 3. Shows percentage change in MEP amplitude vs. baseline 1 minute after active for verum tUS (red) and sham control tUS (blue).

2) Transcranial Ultrasound Stimulation (tUS)

We have been examining the use of tUS for NIBS. TUS offers the capability of modulating brain regions with higher resolution and anatomical specificity than other methods, and also deeper structures with minimal impact on more superficial areas. Low-intensity ultrasound has been used for imaging, opening the possibility that the identical system may be used for both neuroimaging and neurostimulation. To test this, we recently completed a study using a diagnostic ultrasound system

(CX-50, Philips) built for performing ultrasonic imaging. When used in the imaging HGen, B-mode with harmonics on and a focal depth of 10 cm, we found that 2 minutes of stimulation to motor cortex resulted in approximately 6-10 minutes of increased cortical excitation, as evidenced by increased amplitude of transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEPs) recorded from the hand [13] (Figure 3).

3) Transcranial Light Stimulation (tLS)

TLS uses infrared light frequencies that are able to penetrate the scalp and skull, and that modulate neuronal activity and brain function. We have used a system that transmits near-infrared light through the scalp and nasal tissue, with 820 nm light pulsed at 40 Hz for 20 minutes (Gamma Neuro, Vielight). In pilot studies this protocol has been found to accelerate learning and improve performance using the same target learning task as described above, and with a similar effect size to that obtained using tDCS [5-7]. Larger studies are currently being performed to confirm this result, and to use EEG and other neuroimaging modalities to characterize the tLS induced changes brain function that underlie these changes in behavior.

D. Future Prospects Combining NIBS with Neuroimaging

NIBS combined with neuroimaging offers the hope of developing new methods for cognitive enhancement, and new treatments for brain and mental illness that are less expensive and safer than current standards of care. Neuroimaging offers NIBS a procedure to choose among the nearly infinite variety of protocols that are available, and also to better understand the mechanisms by which NIBS works. In return, NIBS may offer a better method to take full advantage of the anatomical and temporal characterizations of healthy cognition contrasted with neurological and psychiatric illnesses obtained using neuroimaging. Together, they may provide new methods for reducing the suffering caused by neurological and psychiatric disorders. Work in our laboratory and others has provided early examples of the successful application of this combined method. Further work may lead to the discovery of new treatments that are able to reduce the impact of brain and mental illness.

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