

Cognitive Neuroscience

1. Highlights

Drs. Michael and Juan Su Terman, in collaboration with Gregory M. Sullivan, M.D., established the first U.S. hospital-based outpatient and inpatient program for light therapy of major depressive disorder, bipolar depression and circadian sleep phase disorders.

2. Staff

Gerard Bruder, Ph.D, Acting Chief

Psychophysiology Laboratory

Gerard Bruder, PhD, Director, Professor of Clinical Psychology
Jürgen Kayser, Ph.D, Associate Professor of Clinical Neuroscience
Craig Tenke, Ph.D, Associate Research Scientist

Cognitive Electrophysiology Laboratory

David Friedman, Ph.D., Director, Professor of Clinical Psychology
Doreen Nessler, Ph.D., Research Scientist II
Marianne de Chastelaine, Ph.D., Research Scientist I

Timing and Cognition Laboratory

Chara Malapani, M.D. PhD, Co-Director, Research Scientist
Peter Balsam, Ph.D., Co-Director, Adjunct Professor of Medical Psychology
Daniela Brunner, Ph.D., Associate Research Scientist
James Towey, Ph.D., Assistant Professor of Clinical Psychology
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Stephen Fairhurst, M.S., Research Scientist IV

Somatosensory and Pain Laboratory

W. Crawford Clark, PhD, Director, Professor of Clinical Psychology
John Kuhl, Ph.D. Research Scientist III
Mieko Hobara, M.A., Research Support Assistant III
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Clinical Chronobiology

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Center of Prevention & Evaluation (COPE)

Cheryl Corcoran, M.D., Irving Assistant Professor of Clinical Psychiatry
Judy Thompson, Ph.D., Fellow

3. Overview

Using behavioral, cognitive, and physiological techniques, the Division of Cognitive Neuroscience investigates brain-behavior relationships and the cognitive and neurobiological mechanisms underlying neuropsychiatric disorders. Research involves basic and preclinical studies, development and application of laboratory-based assessment, and clinical trials. This new division was formed in recognition of the importance of applying new developments in cognitive science to the study of neuropsychiatric disorders that entail significant cognitive dysfunctions. The division comprises units from the prior Biopsychology division-- Psychophysiology, Temporal Cognition, Somatosensory and Pain, Clinical Chronobiology, as well as the Cognitive Electrophysiology Laboratory and the Center of Prevention & Evaluation (COPE). During the past year, the eminent cognitive scientist, Dr. Edward E. Smith, was recruited into the Cognitive Neuroscience Division.

4. Current Research

Psychophysiology Laboratory

The Psychophysiology Laboratory uses quantitative EEG, brain event-related potentials (ERPs), and behavioral measures to study cognitive and neurophysiologic function in schizophrenia and depressive disorders. Drs. Bruder, Tenke and Kayser, in collaboration with the Depression Evaluation Service (DES), continued their NIMH-funded studies of right-left brain asymmetry in depressive disorders. Most recently, they replicated prior findings suggesting the potential of EEG measures of alpha power and asymmetry as predictors of therapeutic response to an SSRI antidepressant and found that these EEG predictors are reliable and stable following treatment. Dichotic listening tests of functional brain asymmetry were also found to predict clinical response to secondary treatment with an antidepressant with a different mechanism of action, i.e., bupropion. As part of Dr. Myrna Weissman's longitudinal, high risk study of depression, grandchildren having both a depressed parent and grandparent showed the same pattern of EEG alpha asymmetry seen in adolescents and adults having a depressive disorder and in offspring of parents concordant for major depression. This supports the hypothesis that the EEG alpha asymmetry represents an endophenotypic marker of vulnerability for a familial form of depression.

Along with members of the Lieber Center, they also continued their NIMH-funded studies of brain event-related potentials (ERPs) and cognitive function in schizophrenia. ERPs recorded during a word serial position test provided evidence that verbal working memory deficits in schizophrenia involve a disturbance of frontal and parietotemporal processes mediating the encoding of working memory representations. An additional study measured brain ERPs of schizophrenic patients and healthy controls during both auditory and visual recognition memory tasks. Cognitive brain potentials over left parietal sites associated with recognition of repeated words were markedly reduced in

schizophrenic patients and midfrontal response-related brain activity was also abnormal in the patients. These findings suggest that deficits in left parietal, medial temporal, and frontal regions underlie poor word recognition memory in schizophrenia. In their current study, brain ERPs of schizophrenic patients and healthy controls are being recorded during both working memory and continuous recognition memory tests with word and face stimuli. The aim is to study the neurophysiology of memory deficits in schizophrenia and to examine whether these deficits are specific to verbal or nonverbal information processing or represent more general deficits in cognitive function. Drs. Kayser and Tenke continued their work developing advanced techniques for processing electrophysiologic data, which are being applied in the above studies of schizophrenia and depression.

In a study of the genetics of working memory in a large sample of 400 healthy adults, we examined two genes that have been associated with risk for schizophrenia and dopamine neurotransmission, i.e. the catechol-O-methyltransferase (COMT) gene and the dopamine D2 receptor (DRD2) gene. The COMT genotypes were associated with performance on working memory tests that require higher-order mental manipulation, but not on tests that measure simple storage of information. Differences in working memory between the DRD2 genotypes were strengthened when the interaction with the COMT polymorphism was included in the analysis. Our findings suggest that an interaction of the DRD2 and COMT genes may be involved in the working memory deficits in schizophrenia.

Cognitive Electrophysiology Laboratory

Dr. David Friedman and his colleagues in the Cognitive Electrophysiology Laboratory are involved in a series of interlocking investigations concerned with cognitive event-related brain potentials (ERPs) recorded from the scalp. Projects covered include memory and attention in normal development, aging, Mild Cognitive Impairment and Alzheimer's disease. A recent addition to ERP neuroimaging has been functional magnetic resonance imaging to investigate the brain regions recruited in the variety of cognitive processes under study. The cognitive aging project is directed at understanding basic memory processes and how they change, in relationship to brain activity, with normal aging. Findings from this NIA-funded project are consistent with deficiencies in frontal lobe function in aging by showing that for the young the requirement to retrieve information about the source of initial learning is accompanied by brain activity over frontal regions. This does not occur for older adults. In addition, studies of attention and aging suggest that the complex function of attentional capture, which also has a frontal-lobe origin, are somewhat compromised with increasing age. In the NICHD-funded project on cognitive development, studies of executive processes implicate immature frontal lobe function as a factor in the lower performance of children compared to young adults. Studies of mild cognitive impairment have been aimed at an understanding whether change in basic memory and executive processes can predict the development of Alzheimer's

disease, an important goal if we are to, eventually, intervene to ameliorate deficits in these ubiquitous processes in individuals with memory and executive disorders.

Timing and Cognition Laboratory

The Timing and Cognition laboratory is a merge of the “Temporal Cognition Laboratory” (from the prior Division of Biopsychology) and the "Adaptive Behavioral Laboratory" (Barnard College). The laboratory studies how time organizes cognition and behavior. The first goal is to create a phenotypic characterization of temporally distorted aspects of learning and behavior that characterize several major neurological and mental disorders, such as depression, drug-abuse, and schizophrenia, as well as Parkinson’s disease and other movement disorders. The second goal is to identify the neural circuitry underlying specific patterns of timing errors associated with distinct behavioral phenotypes and/or diseased entities. The work is an interplay between basic and clinical research and draws on behavioral and cognitive neuroscience, computer modeling, and neuropsychological and psychiatric patient profiling.

Dr. Peter Balsam is supervising the animal research in the lab, which is currently focused on understanding how time is learned and used to guide behavior. One current aim of this work is to help clarify the role of dopaminergic systems in timing behavior. In this NIMH and NIDA supported work, the roles of dopamine in the learning and retrieval of temporal information are being explored. In collaboration with the laboratories of Dr. Eric Kandel (Columbia), Dr. XiaoXi Zhang (University of Chicago), Dr. Marcelo Rubenstein (University of Buenos Aires) and Dr Claudia Schmauss (Columbia and NYSPI), various strains of mice with altered dopaminergic function are being studied in this ongoing research. In a related NIDA funded project the role of dopamine in modulating goal directed and habitual behavior is being investigated in collaboration with Dr. Jon Horvitz (Boston College) and Dr. Mark West (Rutgers University).

Dr. Malapani supervises the human research and the research with patient populations, which is focused on (1) understanding how time is perceived, remembered and used flexibly to guide behavior in humans across the life span (studies with young and aged populations); (2) abnormalities of the time sense in patients with degenerative and mental diseases of the basal ganglia and their cortical targets, especially diseases associated with alterations of the central dopaminergic systems, e.g., Parkinson’s disease (PD), Schizophrenia, Substance Abuse. This research seeks to both understand the basic neural mechanisms of timing and to use cognitive processing as a means of early detection and diagnosis. In collaboration with Pr. John Rinzel and Dr. Eric Brown (New York University, Neural Sciences Department) Dr. Malapani continues modeling the separable encoding and retrieval distortions in PD. The computational modeling work of Parkinsonian timing is seeks to simulate differential effects of dopaminergic pharmacological treatments and Deep Brain Stimulation (DBS) in the subthalamic nucleus or the globus pallidus. This study extends prior work, which showed partial recovery of timing deficits with subthalamic stimulation suggesting the

important role of the indirect striato-pallidal-frontal pathway in temporal cognition.

Dr. Malapani in collaboration with Dr. Towey and Dr Bruder pursued a research direction initiated last year, studying putative deficits in temporal cognition among patients with schizophrenia (SZ). Preliminary results show that compared to normal controls (n=35) time estimates by patients (n=50) when reproducing three target durations were impaired in terms of time reproduction accuracy and also showed increased variability. The project analyzes the effects of medication by comparing medicated to non-medicated patients. Finally, a new study with schizophrenic patients was initiated this year by Dr Balsam and Dr Malapani in collaboration with Dr. Metclafe (Professor of Psychology, Columbia University), by incorporating new timing tasks in the cognitive battery assessing a large cohort of patients at Hillside Hospital.

New lines of human research also aim, in part, at translating basic science into practical application. For example, Dr. Malapani's work on the retrieval distortion associated with PD led to a new line of experiments exploring the role of distinct kinds of feedback in correcting those deficits. This research has also led to a new study that looks at the effects of dopaminergic drugs on timing distortions seen with aging, which is being conducted in collaboration with Drs. Yaakov Stern and Brian Rakitin (Sergievsky Center, Department of Neurology and Cognitive Neuroscience). Using the same timing tasks with young children, college students and healthy seniors, Dr. James Towey has begun to study how the temporal learning and memory changes across the lifespan. In a DARPA funded project in collaboration with Dr. Sarah Lisanby, Dr. Balsam is studying the effects of anticipating transcranial magnetic stimulation. Additionally, Drs. Malapani and Balsam are collaborating with Drs. Carl Hart and Sandra Comer (Columbia University) concerning how drugs of abuse and anticipation of these drugs affects temporal information processing.

Somatosensory and Pain Unit

Dr. Clark and his associates continued several studies aided by a six year NIDCR grant on gender differences in pain sensation and pain report. The medical (or statistical) decision-making procedure was employed to examine the responses of healthy men and women to calibrated noxious and innocuous heat and cold stimuli. No gender differences were found in the values of $P(A)$, a measure of a subject's ability to distinguish among the various stimulus intensities. It was concluded that the neurosensory functioning of men and women are the same, but women set a lower criterion, B , for reporting pain. Reports in the literature that women are more sensitive to pain are due to the inadequate method of serial exploration that is commonly used. The decision-making model makes it clear that women have a different attitude, not a more reactive neurosensory system. Healthy volunteers also rated the intensity of their previous painful experiences on the Pain Experiences Questionnaire (PEQ), which was constructed by our unit. The PEQ lists 42 painful experiences such as toothache, headache, backache,

bone fracture, etc. Scores on the PEQ for women were higher than for men, suggesting that women report more clinical pain than men.

In a study with Dr. Whitehead's group at the University of North Carolina, patients with Irritable Bowel Syndrome (IBS) and healthy controls rated the pain induced by a series of calibrated balloon distensions in the lower colon. Analysis of the data by the medical decision-making model reveal no difference between patients and controls with respect to the neurosensory measure of discriminability, $P(A)$. However, IBS patients do set a much lower pain report criterion, B . That is, they give more reports of pain to the same intensities of stimulation that the controls had received. The result indicates that much greater attention should be paid to treating the psychiatric aspects of the IBS patients' complaint of pain.

The 101-item Multidimensional Affect and Pain Survey (MAPS) was validated by correlating each of its 30 subclusters with the well-established and validated Catastrophizing subscale of the Coping Strategies Questionnaire (CSQ). The CSQ provides a measure of the patient's hopelessness about the course of their illness. Patients suffering advanced cancer showed high correlations among scores on the Catastrophizing subscale and the Emotional Suffering and Somatosensory Pain Superclusters of the 101-item MAPS. The results validate the MAPS and suggest that more attention should be given to the psychiatric treatment of patients with advanced cancer. Two studies using the MAPS were conducted with Dr. Chokhavatia of the Department of Medicine/Gastroenterology, Mount Sinai School of Medicine. Physicians used the MAPS to rate the importance to treatment strategies of various somatosensory and emotional symptoms in their patients. The results demonstrated an almost complete failure of the physicians to consider the emotional and suffering aspects of the patients' illness. In the other study at Mount Sinai, patients with Inflammatory Bowel Disease (IBD) rated the intensity of their symptoms on the MAPS. Compared to IBD patients with active symptoms, IBD patients who were in remission had significantly lower scores on items in the Somatosensory Pain and Emotional Suffering Superclusters. Surprisingly, the patients did not differ on items in the Well-being Supercluster, which is related to quality of life. It was concluded that (a) the MAPS is a valid instrument for assessing both affective and neurosensory aspects of pain, and (b) that IBD patients, even when the disease is active, maintain adequate coping strategies.

Clinical Chronobiology Program

Drs. Michael and Juan Su Terman completed an NIMH-supported six-year study of three nonpharmaceutical treatments for seasonal affective disorder (SAD) – dawn simulation and high-density negative air ionization delivered during sleep, and post-awakening bright light therapy. The findings, published in *American Journal of Psychiatry*, indicated that all three interventions exceeded the placebo rate to low-density ions. The rapidly expanding clinical domain of light therapy to nonseasonal depressions – including treatment-resistant depression first investigated in NYSPI inpatients – was laid out by Dr. Terman in *Sleep Medicine*

Reviews. The Termans also completed an FDA Phase I trial of a new low-dose (0.2 mg) formulation of controlled-release melatonin, designed to facilitate phase-advance shifts of the internal circadian pacemaker system without causing a direct soporific effect. The results demonstrated equivalent timing of washout for both the drug and endogenous pineal melatonin. Dr. Macchi completed an NINDS-supported jet lag study of light-induced circadian rhythm phase advances in preparation for travel from New York to Paris. The results were positive but not impressive, likely due to the phase-advancing effect of natural light exposure upon arrival at the destination. Neither melatonin nor light treatment trials for jet lag adjustment have thus far proved significantly advantageous for travel across six time zones.

Center of Prevention & Evaluation (COPE)

Dr. Corcoran and her colleagues in the Center of Prevention and Evaluation evaluate clinical risk for psychosis in adolescents and young adults, a risk state that is characterized by subtle cognitive effects, affective symptoms, subthreshold positive symptoms, and decrements in social and academic function. COPE has been supported by private (NARSAD, Irving, Pisetsky, Kempf), federal (NIMH), and state funding; it has enrolled nearly 50 subjects thus far. The research goal is to integrate the tools of neuroscience (imaging, genetics, animal models) with clinical research strategies to study evolving symptoms in psychotic disorders. Specific aims of this clinical research program are to 1) characterize this high risk state; 2) identify risk and protective factors; 3) follow markers of evolving illness or symptom resolution; and 4) ultimately, to develop safe and effective services and interventions to prevent the onset of psychosis and improve current function.

A unique focus of COPE, as compared with other clinical high risk programs, is exposure to proximal exposures, such as drug use and stress, and its temporal association with symptoms and function. Dr. Corcoran has found a similar prevalence of drug abuse among high-risk individuals as is found in schizophrenia and other psychotic disorders, with cannabis being the primary drug abused. Further, cannabis use is temporally associated with severity of anxiety and perceptual disturbances, and functional decline. Dr. Thompson, a Pisetsky awardee, has a particular interest in evaluating the stress-diathesis model in evolving psychotic disorder. She has identified prevalent early trauma in at-risk individuals that is correlated with both lower socioeconomic status and positive symptom severity. Dr. Thompson will also prospectively examine the temporal association of affective and positive symptoms with life events in this at-risk group. Further, Dr. Thompson will examine stress-sensitivity in high risk individuals by measuring cortisol reactivity in response to a laboratory stressor and its association with striatal dopamine function, as determined by PET imaging, in collaboration with Dr. Anissa Abi-Dargham.

There are several collaborations with other investigators, both within and outside of the Cognitive Neuroscience Division, to address the specific aims of identifying phenomenology and biomarkers in this prodromal or high-risk period:

Cognitive Neuroscience: With Drs. Bruder, Kayser and Tenke, we are evaluating auditory and olfactory ERPs as potential biomarkers in high-risk patients which may be related also to current symptoms and function.

Neuroimaging: Dr. Bradley Peterson is underwriting and supervising longitudinal multimodal imaging in high-risk teens to identify markers of illness risk and progression. Modes include structural imaging (Dr. Corcoran), spectroscopy (Dr. Larry Kegeles), diffusion tensor imaging (Dr. Tiziano Colibazzi) and functional imaging. Additionally, Drs. Scott Small and Scott Schobel (Neurology) have used MRI with gadolinium to study brain metabolism in both high-risk and schizophrenia patients, identifying abnormal hyperactivity in regions of the hippocampus.

Basic Science: Dr. Holly Moore and her research fellow Dr. Victoria Cressman examine changes in brain circuits in adolescence, both in normal animals and in animal models of schizophrenia. Drs. Moore and Cressman probe the social dysfunction in high-risk adolescents to determine if it is related to social anxiety, social anhedonia, or lack of social skills. Also, Dr. Christoph Kellendonk of Dr. Kandel's laboratory has evaluated behavioral effects of genetic modifications of dopamine receptors in juvenile mice.

Neuropsychology and social cognition: Dr. Ed Smith is a consultant for cognitive assessment of high-risk patients. Dr. Arielle Stanford (Brain Stimulation) has examined emotion recognition and "Theory of Mind" in high-risk patients, and their relationship to symptoms and social function.

Phenomenology: Dr. Andrew Booty (PGY-IV) is undertaking qualitative research with both high-risk patients and family members to understand the evolution of symptoms, and its relation to help-seeking strategies and stigma. Dr. Celine Wong (psychiatrist from Singapore) evaluates burden and stigma among families of high-risk patients. Dr. Paola Mazzoni (child psychiatry resident) studies the distribution of diagnoses among high-risk teens.

Services and treatment: Dr. David Kimhy (of Services) has identified visual processing deficits in prodromal patients and also evaluates delusion development. As a Beck Scholar, he is studying the efficacy of cognitive behavioral therapy in high-risk patients. Dr. Susan Essock (director of Services) has consulted on program development at COPE and its effort to meet the NYS OMH mission of illness prevention.

5. Education and Training

COPE has provided research and clinical training to a number of medical students, psychiatry residents, psychology interns and externs, volunteers and social work students. Visiting fellows have returned to Israel, Singapore and Spain to set up similar early identification clinical research programs. Dr. James Towey continues to direct a unique training program for minority undergraduate students. Most are pre-baccalaureate NRSA fellows who received support from NIMH's Career Opportunities in Research (COR) Training Program. The main objective is to increase the diversity of doctoral-level researchers in mental health fields. Mentors for research training at Psychiatric Institute include Drs. Peter Balsam,

Hector Bird, Adam Bisaga, Gerard Bruder, Madelyn Gould, Christina Hoven, Sarah Lisanby, Bruce Luber, Chara Malapani, John Martin, Michael Myers, Harry Shair and Rikki Waterhouse. Last year, NIMH granted a highly competitive renewal for this training grant, *COR Training of Mercy Scholars at Psychiatric Institute*. Dr Clark is a Mentor to Dr. N. Sonty in the Department of Anesthesiology. Together they are writing a paper and a grant application on low-back pain.

6. Clinical Services

The Center for Light Treatment and Biological Rhythms at Columbia University Medical Center, directed by Dr. Michael Terman, serves a broad national and international patient base with supervision of light treatment both as monotherapy and in conjunction with melatonin or antidepressant medication “treatment as usual.” The Psychophysiology Laboratory records clinical EEGs for inpatient and outpatient services at Psychiatric Institute.

7. Awards and Honors

Dr. Cheryl Corcoran received the Irving Award and Judy Thompson received the Pisetsky Award. Dr. Michael Terman received the inaugural Elliot D. Weitzman Award from the Sleep Research Society for a pharmacokinetic evaluation of his new low-dose melatonin formulation.

8. Bibliography

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