DELUSIONS

A MEDICAL DICTIONARY, BIBLIOGRAPHY,
AND ANNOTATED RESEARCH GUIDE TO
INTERNET REFERENCES

JAMES N. PARKER, M.D.
AND PHILIP M. PARKER, PH.D., EDITORS

ICON Health Publications
ICON Group International, Inc.
4370 La Jolla Village Drive, 4th Floor
San Diego, CA 92122 USA

Printed in the United States of America.

Last digit indicates print number: 10 9 8 7 6 4 5 3 2 1

Publisher, Health Care: Philip Parker, Ph.D.
Editor(s): James Parker, M.D., Philip Parker, Ph.D.

Cataloging-in-Publication Data

Parker, James N., 1961-
Parker, Philip M., 1960-

Delusions: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References / James N. Parker and Philip M. Parker, editors
p. cm.
Includes bibliographical references, glossary, and index.
ISBN: 0-497-00344-9
1. Delusions-Popular works.I. Title.

Disclaimer

This publication is not intended to be used for the diagnosis or treatment of a health problem. It is sold with the understanding that the publisher, editors, and authors are not engaging in the rendering of medical, psychological, financial, legal, or other professional services.

References to any entity, product, service, or source of information that may be contained in this publication should not be considered an endorsement, either direct or implied, by the publisher, editors, or authors. ICON Group International, Inc., the editors, and the authors are not responsible for the content of any Web pages or publications referenced in this publication.

Copyright Notice

Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on delusions. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

About the Editors

James N. Parker, M.D.

Dr. James N. Parker received his Bachelor of Science degree in Psychobiology from the University of California, Riverside and his M.D. from the University of California, San Diego. In addition to authoring numerous research publications, he has lectured at various academic institutions. Dr. Parker is the medical editor for health books by ICON Health Publications.

Philip M. Parker, Ph.D.

Philip M. Parker is the Eli Lilly Chair Professor of Innovation, Business and Society at INSEAD (Fontainebleau, France and Singapore). Dr. Parker has also been Professor at the University of California, San Diego and has taught courses at Harvard University, the Hong Kong University of Science and Technology, the Massachusetts Institute of Technology, Stanford University, and UCLA. Dr. Parker is the associate editor for ICON Health Publications.

About ICON Health Publications

To discover more about ICON Health Publications, simply check with your preferred online booksellers, including Barnes&Noble.com and Amazon.com which currently carry all of our titles. Or, feel free to contact us directly for bulk purchases or institutional discounts:

ICON Group International, Inc.
4370 La Jolla Village Drive, Fourth Floor
San Diego, CA 92122 USA
Fax: 858-546-4341
Web site: **www.icongrouponline.com/health**

Table of Contents

FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with delusions is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about delusions, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to delusions, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on delusions. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to delusions, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on delusions.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON DELUSIONS

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on delusions.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and delusions, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "delusions" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Management of Other Psychiatric States: Hallucinations, Delusions and Other Disturbances**

  Source: Medical Clinics of North America. 78(4): 841-859. July 1994.

  Summary: This article reviews the nature and treatment of some of the noncognitive disturbances among nursing home residents with Alzheimer's disease (AD). It covers studies on the prevalence of behavioral disturbances and their relationship to severity of AD, including neurobiological findings, the risk factors of agitated behavior in people with dementia, the differential diagnosis and treatment of agitated behavior, and the use of various antipsychotics, antidepressants, and mood stabilizers. Final sections cover the prevalence rate and treatment of psychosis. 51 references.

- **Delusions, Delirium, and Cognitive Impairment: The Challenge of Clinical Heterogeneity**

  Source: Journal of the American Geriatrics Society. 40(8): 848-849. August 1992.

  Summary: This editorial discusses the difficulties of studying complex behavioral syndromes, such as those found in Alzheimer's disease. The author suggests that the reason for these difficulties is the heterogeneity of behavioral phenomena. Heterogeneity is also present in dementia. For example, the relationship between severity of cognitive loss and prevalence of psychotic symptoms in persons with Alzheimer's disease seems to vary, depending on clinical subtypes, as defined by age of onset and presence of extrapyramidal signs. In one study, psychotic symptoms were most prevalent in persons with the greatest cognitive impairment, but this was not always the case. Persons whose dementia began prior to age 65 and those who manifested extrapyramidal signs had **delusions** even when mildly impaired. There are also studies that suggest that demented patients with **delusions** have biological features that distinguish them from demented patients without **delusions.** The author notes that delirium, like dementia, is polymorphic in its manifestations. Acknowledging that heterogeneity exists and attempting to understand its sources can help improve understanding of the mechanisms underlying **delusions,** delirium, and other behavioral disturbances. 13 references.

- **Delusions and Hallucinations in an Adult Day Care Population: A Longitudinal Study**

  Source: American Journal of Geriatric Psychiatry. 6(2): 104-121. Spring 1998.

  Summary: This journal article describes a study funded by the National Institute on Aging of the prevalence and correlates of **delusions** and hallucinations among older people attending adult day-care centers. The sample consisted of 200 participants, aged 60-97 years, at 5 adult day-care centers in Montgomery County, Maryland. The average education was 12.3 years, and average length of day-care attendance was 1.4 years; 87.5 percent were white and 66 percent were female. The participants were assessed at 6-month intervals for the presence of **delusions** and hallucinations, medical status, pain, agitation, depressed affect, and cognitive functioning. The prevalence of **delusions** was 13.8 percent as reported by staff and 36.4 percent by relatives; the prevalence of hallucinations was 6.1 percent as reported by staff and 27.3 percent by relatives. **Delusions** and hallucinations were more likely to occur in residents with depressed affect, agitation, and dementia, particularly those with Alzheimer's disease, those with moderately severe to severe dementia, and those with worsening dementia. The authors conclude that **delusions** and hallucinations occur in a substantial proportion of adult day-care participants and are associated with several other pathologies, including dementia. 2 figures, 5 tables, 40 references.

- **Risk of Mortality and Institutionalization in Demented Patients With Delusions**

  Source: Journal of Geriatric Psychiatry and Neurology. 9(3): 123-126. July 1996.

  Summary: This journal article describes an Italian study of the risk of mortality and institutionalization in patients with dementia who have **delusions.** A sample of 99 patients with dementia were enrolled in the study and followed for 2 years after discharge from an Alzheimer's disease (AD) unit. Sixty-seven patients were diagnosed with AD and 32 with multi-infarct dementia. Dementia severity was measured with the Global Deterioration Scale. Cognitive status was assessed by a comprehensive battery of neuropsychiatric tests including the Mini-Mental State Examination. Functional status

was assessed with Katz's Activity of Daily Living Scale. The presence of **delusions** was determined from the medical charts. Two years after discharge, information about survival and admission to a nursing home was obtained from a telephone interview with the primary caregiver for 87 patients. Twenty-three patients died over the 2-year followup period. The mortality rate was not significantly different between patients with and without **delusions** at baseline. However, patients with **delusions** at baseline were significantly more likely to be institutionalized than were those without **delusions** (56.0 percent versus 25.8 percent). The risks for mortality and institutionalization did not change after adjusting for age, education, and level of functional and cognitive impairment. These findings suggest that the presence of **delusions** may predict future institutionalization in people with dementia. 2 tables, 30 references.

- **Delusions, Hallucinations and Depression in Alzheimer's Disease: A Biological Perspective**

  Source: American Journal of Alzheimer's Care and Related Disorders and Research. 6(3): 21-28. May-June 1991.

  Contact: Available from Prime National Publishing Corp. 470 Boston Post Road, Weston, MA 02193. (617) 899-2702. PRICE: Single issue $8.00. Call for information.

  Summary: This journal article discusses, from a biological perspective, three symptoms that complicate Alzheimer's disease: **delusions,** hallucinations, and depression. Relevant clinical, neuroradiological, neuropathological, sensory impairment, and genetic data are reviewed concerning the possible biological mechanisms underlying the three behaviors and the behaviors' relationship to the Alzheimer's disease process. In addition, the pharmacological and physical treatments of these behaviors are discussed, including the fact that hallucinations seem to be less amenable to pharmacological treatment than are **delusions.** The findings of relevant research studies are discussed, and areas for future research are suggested. It is concluded that currently, hypotheses on the pathophysiology of these three complicating behaviors remain speculative and more data are needed if their etiology is to be clarified. 57 references.

- **Clinical Perspectives: What Should We Be Studying? Delusions**

  Source: International Psychogeriatrics. 8(Supplement 3): 383-385. 1996.

  Summary: This journal article highlights findings from the authors' studies of **delusions** in patients with Alzheimer's disease (AD) and other dementias admitted to the Alzheimer's unit of the Fatebenefratelli Hospital in Brescia, Italy. In one study, the authors found that **delusions** occurred in 45-percent of patients with AD and 38-percent of those with multiinfarct dementia (MID). In a separate study of 102 consecutive outpatients with AD, the prevalence of **delusions** was 42-percent and did not vary across patients with mild, moderate, or severe dementia. However, the hallucinations increased significantly in later, more severe stages of AD. Another sample of 67 patients with AD and 32 with MID was studied to explore the relationship between **delusions** and clinical and computed tomographic findings. The authors found that focal lesions in the frontal areas were the only variable that appeared to be significantly and independently associated with delusional symptoms. The data suggest that the anatomic changes correlated with **delusions** are different from those related to cognitive impairment. In a prospective study of the prognostic relevance of **delusions,** the authors found that the presence of **delusions** in patients at baseline was a significant predictor of subsequent institutionalization but not mortality. The authors conclude that more than 40-percent of patients with dementia will become delusional during their illness, but

that patients with **delusions** are no more likely to die than those without **delusions.** 1 table, 5 references.

- **Hallucinations, Delusions, and Cognitive Decline in Alzheimer's Disease**

  Source: Journal of Neurology, Neurosurgery and Psychiatry. 69: 172-177. 2000.

  Summary: This journal article investigated the occurrence of **delusions** and hallucinations in people with Alzheimer's disease (AD), noting their relationship to the rate of cognitive decline. Participants completed annual clinical evaluations over four years. Results indicated that at baseline, 55 percent of participants had **delusions,** and 41 percent had hallucinations. When controlling for baseline level of cognitive function, demographics, parkinsonism, and use of antipsychotic medications, hallucinations related to a more rapid cognitive decline. This effect related to a subgroup with both visual and auditory hallucinations. The researchers concluded that hallucinations are selectively related to more rapid cognitive decline in people with AD. 2 figures, 2 tables, 34 references.

- **Delusions and Behavioral Disturbances in Cognitively Impaired Elderly Persons**

  Source: Journal of the American Geriatrics Society. 40(8): 768-773. August 1992.

  Summary: This journal article reports a study that found that **delusions** in persons with Alzheimer's disease or other dementia are associated with a variety of behavioral problems. The study utilized a retrospective review of the medical records of 114 outpatients with diagnoses of either Alzheimer's disease, multi-infarct dementia, or a mix of the two. **Delusions** were reported for 25.5 percent of the patients. Several behavioral disturbances were more common in delusional than in nondelusional patients, including agitation, angry or hostile outbursts, urinary incontinence, wandering or pacing, and insomnia. Delusional and nondelusional patients had similar cognitive function as measured by the Mini-Mental State Exam, although there was a statistically borderline tendency for **delusions** to occur more often in patients in the midrange of cognitive impairment. 29 references.

- **Incidence of and Risk Factors for Hallucinations and Delusions in Patients With Probable AD**

  Source: Neurology. 54: 1965-1971. May 2000.

  Summary: This journal article reports on a study that investigated the incidence of and risk factors for **delusions** and hallucinations in people with probable Alzheimer's disease (AD). Researchers conducted psychiatric evaluations of 329 people with probable AD using data from annual clinical and neuropsychological evaluations to determine whether there were specific risk factors for developing **delusions** and hallucinations. Analysis indicated that the cumulative incidence rates for hallucinations and **delusions** increased over four annual post- baseline evaluations. Significant predictors included exaggerated semantic memory decline, exaggerated general cognitive decline, bradyphrenia, and Parkinsonian gait. Age, education, and gender were not significant predictors. 1 figure, 3 tables, 46 references.

- **Delusions in Dementia: A Review**

  Source: Journal of Neuropsychiatry. 3(2): 121-130. Spring 1991.

  Summary: This journal article reviews **delusions** that complicate dementia. According to the author, **delusions,** hallucinations, agitation, wandering, insomnia, and noisiness

must be studied separately to understand their physiopathology and nature in order to effectively manage dementia. Six areas pertaining to **delusions** in dementia are reviewed: nosology, phenomenology, epidemiology, clinical characteristics and correlations (including cognition, depression, and sensory deficits), treatment with antipsychotic medications, course and prognosis. Reports of studies dating as far back as 1955 were reviewed. The author notes that the study of one particular complication of dementia, **delusion,** illustrates current deficiencies of knowledge in some areas. The author asserts that postmortem studies are needed to understand the mechanisms that underlie psychotic symptoms in dementia. 90 references.

Federally Funded Research on Delusions

The U.S. Government supports a variety of research studies relating to delusions. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to delusions.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore delusions. The following is typical of the type of information found when searching the CRISP database for delusions:

- **Project Title: A THYROID RECEPTOR CO-ACTIVATOR HYPOTHESIS FOR PSYCHOSIS**

  Principal Investigator & Institution: Philibert, Robert A.; Psychiatry; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2002; Project Start 01-JAN-2002; Project End 31-DEC-2005

  Summary: (provided by applicant) Schizophrenia is a neurodevelopmental syndrome that affects approximately 1 percent of the U.S. population and is characterized by the presence of hallucinations and **delusions.** Genetic factors are thought to account for the majority of the vulnerability to illness for this syndrome. These genetic factors are thought to be composed of major, moderate ant mild effect loci. The identification and characterization of genetic factors of even mild effect loci is a critical step in the process of understanding the pathogenesis of this group of disorders. In prior moleular studies, the candidate has identified an exonic polymorphism (HOPA12bP) in a critical portion of a gene for a thyroid receptor co-activator named HOPAthat is associated with a behavioral endophenotype that include schizophrenia and hypothyroidism. In this five year training grant, the candidate proposes to focus on the behavioral syndrome that is associated with the polymorphism and 1) demonstrate segregation of the polymorphism with illness. 2 refine the phenotype associated with the polymorphism, and 3) identify

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

other mutations that may be related to illness. Scientific Aims of this grant are 1). Peform case control analyses on schizophrenic probands with the HOPA12bp polymorphism. Schizophrenic HOPA probands will be identified and compared to matched case controls for cognitive/behavioral, endocrinological and medical differences. 2. Conduct a focused linkage study of the families of HOPA12bp probands. Structured interviews will be used to assess the presence of cognitive/behavioral and medical co-morbidity in the first-degree relatives of control and HOPA12bP probands. These results will be correlated with genetic status. 3). Conduct SSCP analysis across the HOPA Gene to detect other potentially pathogenic mutations. Mutation analysis will be performed using DNA from other schizophrenic patients to detect other mutations in theHOPA gene that can result in result in this syndrome or related phenotypes. Training Aims of this grant are to 1) develop clinical skills in the diagnosis and standardized measurement of complex behavior and endocrinological disorders, and 2) learn medical and psychiatric epidemiology, ethics, and biostatistical approaches to complex disorders. The net effect will be to produce an independent investigator capable of functional and translational research.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: AMPAKINES IN SCHIZOPHRENIA**

  Principal Investigator & Institution: Johnson, Steven A.; Senior Scientist; Cortex Pharmaceuticals, Inc. 15231 Barranca Pkwy Irvine, Ca 926182201

  Timing: Fiscal Year 2002; Project Start 01-FEB-1999; Project End 31-AUG-2004

  Summary: (Adapted From the Applicant's Abstract) Currently available antipsychotics effectively control positive symptoms (hallucinations, delusions), but persistent negative symptoms (withdrawal, apathy) and cognitive deficits are little affected and can be quite disabling in most patients with schizophrenia. Recently, a new class of orally-bioavailable molecule that specifically enhances AMPA-type glutamate receptor activity has been developed. AMPAKINES facilitate acquisition and retention of memory in rodents and humans, and synergistically interact with modern antipsychotics. We recently completed an exploratory safety trial of the AMPAKINE CX516 added to clozapine in 19 treatment-resistant patients. CX516 was well tolerated and produced consistent improvements in negative symptoms, attention, and memory. We now propose to conduct a larger, placebo-controlled trial of CX516 added to olanzapine in patients with schizophrenia. The primary hypothesis is that CX516 will improve negative symptoms, attention, and verbal memory. Secondary aims are: 1) to asses the safety and tolerability of CX516 compared to placebo in olanzapine-treated patients; 2) to assess CX516 effects on positive symptoms, anxiety, depressive symptoms, executive function, and verbal fluency; and 3) to assess effects on extrapyramidal symptoms, including parkinsonism, akathisia and tardive dyskinesia. Positive effects on clinical (negative, positive, extrapyramidal) and neuropsychological (cognition, memory, attention) symptoms in a larger trial will strongly suggest that AMPAKINES may be useful for treatment of schizophrenia. PROPOSED COMMERCIAL APPLICATION: This research may lead to the development of a new, improved class of antipsychotic drug for schizophrenia. These new drugs have the potential to treat the diverse symptoms of this complex disease.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CANNABINOIDS AND CORTICAL-CEREBELLAR FUNCTION**

  Principal Investigator & Institution: Patel, Sachin; Pharmacology and Toxicology; Medical College of Wisconsin Po Box26509 Milwaukee, Wi 532260509

Timing: Fiscal Year 2002; Project Start 01-JUL-2002

Summary: (provided by applicant): Cannabis intoxication is known to produce psychotic symptoms such as **delusions,** and disorganized thoughts resembling schizophrenia. In addition, epidemiological data supports a correlation between cannabis use and subsequent development and/or exacerbation of schizophrenia in humans. Schizophrenia is known to inhibit the activity of prefrontal-thalamic-cerebellar network in humans, and has led to the cognitive dysmetria hypothesis of schizophrenia. This posits that a primary dysfunction in the prefrontal-thalamic-cerebellar network underlies the broad range of schizophrenic symptomatology. We will utilize functional magnetic resonance imaging, Fos immunohistochemistry and mass spectroscopy to explore the biological mechanisms by which cannabinoids may inhibit prefrontal-thalamic-cerebellar networks in animals with the aim of further understanding the biological basis for the high correlation between cannabis use and schizophrenia. In addition, we plan to evaluate the role of the endogenous cannabinergic system in the regulation of the prefrontal-thalamic-cerebellar network. We hope that successful completion of these studies will provide enhanced understanding of both the endocannabinoid system and its possible contribution to the pathophysiology of schizophrenia.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: CORE--COMPUTATIONAL NEUROSCIENCE**

  Principal Investigator & Institution: Hasselmo, Michael E.; Professor; Harvard University (Medical School) Medical School Campus Boston, Ma 02115

  Timing: Fiscal Year 2002

  Summary: PRIMARY UNIFYING HYPOTHESES: The Computational Core is guided by three main unifying hypotheses. These hypotheses are as follows: 1.) a decrease in feedback inhibition due to loss of NMDA receptor activation on interneurons should contribute to greater spread of excitatory associative activity in models of region CA3, 3.) a decrease in perforant path input to hippocampus should prevent the matching mechanism in region CA1 (and subiculum) which normally regulates the nature of representations spreading along feedback connections to the neocortex. These two physiological level hypotheses underlie the third hypothesis: 3.) increased associative spread and decreased including **delusions,** hallucinations and loosening of associations, as well as certain negative symptoms, such as impaired memory performance. This would result from activity spread causing strengthening of erroneous associations, and lack of effective matching allowing erroneous representations to become consolidated in neocortex due to consolidation mechanisms summarized in a recent review. The process of matching has been analyzed extensively in the Hasselmo laboratory. Detailed modeling in the Computational Core will address hypotheses concerning the specific projects in this grant, linking the cellular, systems and behavioral levels. These include testing how NAAG effects could decrease Sternberg task performance, and D-cycloserine could increase performance (negative symptoms testing in Project VI), testing how NAAG effects could decrease verbal recall (negative symptoms studied in Project V), testing how NAAG and DA effects a perforant path input could underlie positive symptoms of schizophrenia (relating to physiological parameters studied in Projects II and II), testing how loss of GABAergic modulation could increases in place field size and decrease in sensitivity to cue rotation (relating the GABAergic parameters to place cell recording in Project I), and testing how differential sensitivity of interneuron NMDA receptors to NAAG could underlie both positive and negative symptoms (relating to physiological parameters tested in Project III).

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FMRI LOCALIZATION OF PSYCHOTIC SYMPTOMS IN SCHIZOPHRENIA**

  Principal Investigator & Institution: Silbersweig, David A.; Associate Professor; Psychiatry; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2002; Project Start 08-AUG-2002; Project End 31-JUL-2006

  Summary: (provided by applicant): Schizophrenia is a devastating and common disorder, affecting 1% of the population worldwide, and causing tremendous suffering at great societal cost. Psychosis, consisting of the symptoms of **delusions** and-hallucinations, represents the most striking and severe part of the psychiatric symptom spectrum, and causes significant morbidity. Nevertheless, less is known about the pathophysiology of such positive symptoms, compared with the widely studied deficit or negative symptoms. Functional neuroimaging is uniquely suited to an in vivo, systems-level investigation of psychiatric disorders, and can be adapted for the study of psychosis. Functional magnetic resonance imaging (fMRI) methods are now mature enough to reliably take advantage of the increased spatial and temporal resolution offered by this technology. The investigators have optimized methods of fMRI study design, image acquisition and analysis for the study of psychotic symptoms. They have also developed behavioral activation paradigms to target the specific neural circuits and neuropsychological functions implicated in these symptoms, based upon their previous work, in the context of current knowledge in the field. In this project these methods will be used with well-characterized, actively paranoid schizophrenic patients as well as non-psychotic patient and normal control subjects, to identify and characterize patterns of neural activity associated with the prominent psychotic symptom of paranoid **delusions,** and to test a neurobiologically specific model of psychosis in schizophrenia. This model is closely integrated with basic neuroscientific models and experiments, and focuses upon increased activity in mesotemporal and subcortical mesolimbic structures, in the setting of decreased activity in medial prefrontal regions. Such a neurobiological characterization of the major psychotic symptoms can increase our understanding of the pathophysiology of schizophrenia, and thereby provide a necessary foundation for the development of more targeted, biologically based diagnostic and therapeutic strategies.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LSD AND SEROTONIN RECEPTOR FUNCTION**

  Principal Investigator & Institution: Gresch, Paul J.; Pharmacology; Vanderbilt University 3319 West End Ave. Nashville, Tn 372036917

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002

  Summary: Provided by applicant): Schizophrenia is a psychiatric disorder with core symptoms that include **delusions,** disorganized thought and speech, and hallucinations. The neural substrate for the formation of hallucinations is, at present, unclear. In this application, biochemical and behavioral experiments will be performed to examine the loci of action of the hallucinogenic drug lysergic acid diethylamide (LSD). LSD is thought to mediate its actions primarily through serotonin-2A (5-HT2a) and serotonin-2C (5-HT2c) receptors. Specific Aim I will examine the contribution of 5-HT2A and 5-HT2c receptors to the induction of the immediate early gene, c-fos, in rat brain after LSD treatment. Specific Aim H will utilize direct microinfusion to isolate which brain site(s) are involve in the LSD-induced discriminative stimulus. Finally, Specific Aim Ill will examine whether there are functional alterations of 5-HT2A and 5-HT2c receptors after

repeated LSD exposure. A long-term goal is to understand the neuronal mechanism of action of LSD, a potent hallucinogen, and how these neuronal processes might be dysfunctional in a disease state such as schizophrenia.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MALADAPTIVE BEHAVIORS & ALZHEIMERS DISEASE IN ADULTS WITH DOWN SYNDROME**

  Principal Investigator & Institution: Urv, Tiina K.; New York State Office of Mental Health 44 Holland Ave Albany, Ny 12229

  Timing: Fiscal Year 2003; Project Start 26-SEP-2003; Project End 31-AUG-2008

  Summary: The overall aim of Subproject 2 is to determine the relationship of maladaptive behaviors with the development and progression of Alzheimer's disease (AD) in adults with Down syndrome (DS). Studies in the general population have found a spectrum ofmaladaptive behaviors that many individuals with AD display prior to onset and during its progression. The appearance of specific maladaptive behaviors in the elderly may be an early indicator of the onset of dementia. Different types of maladaptive behaviors (e.g., aggression, anxiety, and delusions) have been found to be heterogeneous, both in the type and timing of presentation during the course of AD. Clarification of the different pattems of the various types of maladaptive behaviors in relation to AD onset, and the association of specific maladaptive behaviors with different stages of AD may provide valuable insights into diagnosis, treatment for individuals with DS. Few studies have investigated the types maladaptive behaviors associated with AD in adults with DS. Our preliminary work suggests that the presentation of AD in this population may be atypical and that maladaptive behaviors may be among the earliest detectable signs of dementia onset. However, there have been no longitudinal studies conducted explicitly to determine the types of maladaptive behaviors associated with the onset of dementia and with their persistence and severity throughout the progression of AD. In this study we will determine longitudinally how maladaptive behaviors are related to dementia onset and progression and examine how maladaptive behaviors vary with the presence of specific factors such as sex, level of mental retardation and whether or not psychoactive medications are prescribed, in 338 adults with DS. The results of this study will broaden the scope of measures for screening and early detection of AD in DS and will have implications for prevention and therapeutic interventions.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: MOLECULAR PHARMACOLOGY OF PSYCHOSIS RISK IN AD**

  Principal Investigator & Institution: Sweet, Robert; Scientist; University of Pittsburgh at Pittsburgh 350 Thackeray Hall Pittsburgh, Pa 15260

  Timing: Fiscal Year 2002

  Summary: The psychotic symptoms, **delusions** and hallucinations, are present in at least 30-40% of patients with Alzheimer's disease (AD). Psychotic symptoms in AD patients (AD+P) predict more rapid functional decline and premature institutionalization. Current treatments for AD+P are inadequate. We have hypothesized a polygenic model of AD+P. In preliminary tests of this hypothesis of this hypothesis, we have found that AD+P was significantly more frequent in patients with specific genotypes at the dopamine1 (D1) and D3 receptor loci (Sweet et a., 1998). Similarly, Holmes et al. (1998) reported an association in AD patients with variation in the serotonin/2A (5-HT2A) and 5-HT2C receptor genes. We propose to establish a cohort of 644 subjects, prospectively

and longitudinally characterized with regard to psychosis phenotype, for examination of the genetic determinants of AD+P. Subjects with mild cognitive impairment, possible AD and probable AD will be evaluated at presentation to the Alzheimer's Disease Research Centers of the University of Pittsburgh and the University of Pennsylvania. Genetic material will be obtained. Neuropsychiatric assessments of psychotic symptoms will be conducted, with ratings on the CERAD Behavioral Rating Scale. Subjects without current or prior psychotic symptoms will be followed longitudinally with repeat assessments for psychotic symptoms every 6 months. Telephone assessments will be used for subjects unable to return to minimize incomplete data due to drop-outs. We project 20%-30% of the 644 subjects without psychosis at baseline will develop incident AD+P during the study interval. We hypothesize: 1) D1 receptor genotype will predict onset of AD+P; 2) D3 receptor genotype will predict onset of AD+P; 3) 5-HT2A receptor genotype will predict onset of visual hallucinations; 4) H-HT2C receptor genotype will predict onset of visual hallucinations. This study would be the first to prospectively evaluate the contribution of specific genes to predicting the onset of psychotic symptoms in any disorder. Replicated findings would provide a compelling rationale for family-based studies to address population stratification effects and for pursuit of the identified receptors as targets for drug development. Finally, establishing an AD cohort with prospectively determined psychosis phenotype will facilitate the research for novel risk genes as new genetic technologies become available.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: NEURAL CORRELATES OF SOURCE MONITORING IN SCHIZOPHRENIA**

  Principal Investigator & Institution: Weiss, Anthony P.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2003; Project Start 01-FEB-2003; Project End 31-JAN-2008

  Summary: (provided by applicant): This is an application for an NIMH Mentored Patient-Oriented Research Career Development Award (K-23), entitled "Neural Correlates of Source Monitoring in Schizophrenia." The candidate's interest is in understanding the neural basis for the aberrant memory processes seen in schizophrenia, with an eventual goal of examining the role of these faulty cognitive processes in the production of hallucinations and **delusions.** In addition to the proposed research described below, the candidate seeks training in functional neuroimaging acquisition and analysis, the cognitive psychology of abnormal memory, and the conduct of ethical clinical research. The proposed research plan, didactic courses, and tutorial instruction from mentors and advisors will serve to foster the candidate's development into an independent clinical researcher in the functional neuroimaging of schizophrenia. Schizophrenia is associated with a particular type of memory disturbance, with intact old/new recognition (i.e., deciding whether an event had occurred previously), but impaired recollection of the contextual details of an experienced event. With limited contextual memory, these patients show deficits in source monitoring, the ability to specify the origin of recollected events. Thus, they may recognize an event as familiar, but have difficulty determining whether the recollected event was actually witnessed, or simply imagined. Although old/new recognition and source monitoring rely on similar neural regions, namely the hippocampus and prefrontal cortex (PFC), source monitoring requires greater activity in these regions. Intact old/new recognition with aberrant source monitoring, as seen in schizophrenia, may therefore indicate that the hippocampaI-PFC network is functioning, but is unable to up-regulate its activity in the face of greater cognitive demands. The proposed