



MASSACHUSETTS  
GENERAL HOSPITAL



BRIGHAM AND  
WOMEN'S HOSPITAL



HARVARD  
MEDICAL SCHOOL

## MESSAGE FROM THE CHIEF

**T**HE BOSTON AREA is a thriving hotbed for some of the most cutting-edge R & D ('research & development') institutions in the world, and one metric that we can count on for our ongoing success is our ability to serve as a mecca in attracting the most talented researchers and clinicians to 'Beantown' to tackle complex diseases that require multi-disciplinary ingenuity. In this issue of our newsletter, we are pleased to provide snapshots of some of the avant-garde research projects we're conducting, driven by the energy of our investigators. I hope you will enjoy our interview with neuropsychologist - Dr. Dorene Rentz - where she describes her research on uncovering the silent changes in the brain that may signify the onset of a dementing illness, and Dr. Mark Albers' description of his pioneering studies on smell function (olfaction) and neurodegenerative diseases. Our popular Guest Column returns with a highlight on MGH pediatric neurologist Dr. Florence Lai's fascinating research with individuals with Down syndrome at McLean Hospital in Belmont.

It was a hectic yet productive year for us on the MGH campus. We submitted our 5-year grant renewal application to the National Institute on Aging (NIA), which included an exciting new project taking advantage of new technology from our colleagues at the Athinoula A. Martinos Center for Biomedical Imaging ([www.nmr.mgh.harvard.edu](http://www.nmr.mgh.harvard.edu)). This project uses the ambitious National Institutes of Health (NIH) Human Connectome Project to map the human brain's neural connections in their entirety with next-generation sophisticated scanners (check out the gallery of incredible images from 'Diffusion Spectrum Imaging (DSI)' techniques available at [www.humanconnectomeproject.org/gallery/](http://www.humanconnectomeproject.org/gallery/)). New imaging and other new ways to help make the diagnosis of different dementing diseases, and new ways of learning about how they affect the brain, have given us unprecedented opportunities - at the same time that the sequestration at the National Institutes of Health has led to budget cuts from our major source of support. In response, we are tightening our belts, and trying to find ways to keep the studies moving at full speed more efficiently - sometimes by switching to phone interviews, and sometimes by reassessing the number of individuals we need for various projects. We are committed to doing everything we can to make sure that the research pushes ahead as fast as possible. We know also that none of our advances could be accomplished without your precious investment of time, resources and effort, and I thank you once again for our incredible partnership.

*Bradley J. Hyman*

Brad

# Keep in MiND!

A NEWSLETTER FOR FRIENDS AND SUPPORTERS  
OF THE MASSACHUSETTS ALZHEIMER'S DISEASE  
RESEARCH CENTER AND THE MEMORY STUDY

[www.madrc.org](http://www.madrc.org)



Dr. Hyman

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Fall/Winter 2013 Vol. 4 Issue 1

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**WAYS TO GIVE**

For information about ways to support the clinical care, research, teaching and community health activities of the Massachusetts ADRC, please contact Liang Yap at 617.726.3987 or

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The screenshot shows a computer browser displaying the Massachusetts Alzheimer's Disease Research Center website. The page features a banner with a bridge and city skyline, followed by sections for 'HISTORY & MISSION', 'LEADERSHIP', and 'DEMENTIA IN THE NEWS'. A sidebar on the right includes links for 'About', 'People', 'Research', 'Education, Training & Outreach', 'Patient & Caregiver', 'Participate', 'Contact Us', and 'Media/Phone/Email'.

## Diagnosis Through Sense of Smell

by Mark W. Albers, MD, PhD

*"The act of smelling something, anything, is remarkably like the act of thinking. Immediately at the moment of perception, you can feel the mind going to work, sending the odor around from place to place, setting off complex repertoires through the brain, polling one center after another for signs of recognition, for old memories and old connection."*

— Lewis Thomas (1913-1993, American physician)

**THE VAST MAJORITY** of people afflicted with Alzheimer's Disease (AD) and Parkinson's Disease (PD) exhibit deficits in their ability to identify odors. Most patients with AD do not experience or report a change in their smell function, and most patients who develop olfactory deficits have disorders of the nose and not disorders of the brain. We seek to determine if differences in the brain's processing of olfactory input in preclinical (or asymptomatic) individuals predicts the onset of symptoms of these neurodegenerative diseases. Teaming with Lloyd Hastings, an engineer who developed a portable olfactometer that permits testing in clinical research, outpatient clinic, inpatient, and home settings, we developed novel probes of human olfactory

function. To date, we have tested over 180 individuals, many recruited from the Longitudinal Cohort of the ADRC at MGH. After analysis of our results with biostatisticians affiliated with the ADRC, our initial results are promising! We have presented them recently at the annual meetings of the American Academy of

Neurology and the Alzheimer's Association International Conference. We will continue our studies by following the tested individuals over time, assessing their cognitive and olfactory functions. We are actively recruiting additional participants for this study. Our overall aim is to develop and validate a non-invasive and cost-effective biomarker to identify individuals at risk for developing symptoms of neurodegenerative disease. ♦



Image courtesy of Osmic Enterprises, Inc.



Dr. Albers

# A Conversation with Dorene M. Rentz, PsyD

**Dr. Rentz, you are a clinical neuropsychologist with a fascinating undergraduate degree in theology and philosophy. Tell us something about your background, and how the work of a neuropsychologist is similar to, or different from, that of a clinical psychologist or psychotherapist?**

**DR. RENTZ:**

Thanks for the opportunity to address the MADRC community. I came into neuropsychology later in life. As you mentioned, my first degree was in theology and philosophy

and for the first 18 years of my career, I taught ascetical/mystical theology at Tolentine Center in Chicago, IL specializing in the written works of Teresa of Avila and John of the Cross. I worked closely with a Patristic Scholar, Fr. Jerry Kries, OSA and had the opportunity to teach, give retreats and provide spiritual direction to adults. It was this background that led me into the field of clinical psychology.

At that time, I was

vitally interested in understanding the differences between mystical experience and psychosis. However, early on in my studies for the Doctorate in Clinical Psychology, I became acquainted with Dr. Mark Moulthrop, a neuropsychologist at the University of Chicago. He became my dissertation advisor and sparked my interest in Alzheimer's disease. This was 1982 and neuropsychology was a brand new specialty in the field of clinical psychology. I became fascinated with brain-behavior relationships and have dedicated my life to this career ever since. A neuropsychologist is different from a traditional clinical psychologist because of the in-depth understanding of neuroanatomy, brain-behavior relationships and the differential diagnosis of various neurological disorders that affect the brain. Most of my clinical work is in the cognitive testing of patients, which assists in the

diagnosis of the neurological disorder. This is particularly true for various dementing disorders, such as Alzheimer's disease, Frontotemporal dementia, Vascular Dementia and Parkinson's disease where the clinical changes in the brain may vary. While I am a skilled psychotherapist and provide empathy and behavioral interventions to my patients, that is not the main focus of my clinical career.

**What are some of your research interests, and how did you come to develop your passion in these areas?**

**DR. RENTZ:**

My main research interest is in the detection of the earliest changes of Alzheimer's disease, particularly in high functioning individuals. I developed a passion in this area because I believe that individuals who are highly educated or intelligent would continue to perform normally on cognitive tests long after Alzheimer's disease begins in the brain. This factor would make these individuals most at risk for not receiving early treatment, if it was available. This became apparent to me when I was a student at the University of Chicago. I had the opportunity to evaluate the founder of a specialized form of mathematics that became the basis for all computer languages. He even received the Congressional Gold Medal from President Ronald Reagan for this work. However, his colleagues brought him into the clinic because he was getting lost on his way to his office at the University of Chicago. He performed normally on my testing and the head of the clinic told his colleagues that he was "normal." I'll never forget his colleague who exclaimed, "But doctor, you don't understand, this man is brilliant." It was the first time I realized that those who were high functioning were at the greatest risk for being called "normal" when they were not. Since then, we now have imaging methods that allow us to see the earliest changes of Alzheimer's disease in the brain, but I continue to develop more cost-effect, cognitive methods for detecting these earliest changes.

**Is Alzheimer's disease an 'old-age' disease that only occurs in people who are fifty years or older, or is it now possible to detect changes in the brain in adults who may be in their twenties, thirties or forties? What is some of the innovative research that you and your colleagues are engaged in to detect such 'silent changes' in people who may be most vulnerable to developing the disease?**

## DR. RENTZ:

There are two genetic strands of Alzheimer's disease, a familial dominant form that may begin early in life. These individuals may begin to show signs of memory loss during the ages of 30 to 50. There is also a sporadic variety of the disease that begins later in life, usually during the ages of 70 to 90. This is the most common form of the disease affecting most individuals. Statistics show that 30 to 40 percent of people aged 80 or greater are at risk for Alzheimer's disease.

We now know that the brain changes of Alzheimer's disease may begin 15 years prior to the emergence of memory loss. These findings have been confirmed, not only by autopsy but also by amyloid imaging using Positron Emission Tomography (PET). Recently, Dr. Keith Johnson has also started using a new PET tracer that attaches to Tau in the brain. This is very exciting for us, because we now can see both amyloid and tau - the two major changes of Alzheimer's disease in the brain of living individuals. This will allow us to determine if the earliest "silent changes" are really associated with amyloid, tau or a combination of both, when individuals are still clinically normal.

Over the past 4 years, we have been following a large cohort of 250 subjects in the Harvard Aging Brain Study that is being led by Dr. Reisa Sperling, a MADRC investigator. Some of the subjects in this study are also in the MADRC. These generous subjects have volunteered to undergo cognitive testing, as well as MRI and PET imaging to help us uncover the secrets of this devastating disease that is affecting many older adults. As a result of this study, we will be beginning a new clinical trial for the prevention of Alzheimer's disease called the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Trial or A4 trial. This clinical trial is for people who show the earliest changes of amyloid in the brain but are still functioning normally on cognitive testing. We believe that if we can remove the changes of amyloid before individuals become forgetful, than we may prevent them from ever developing Alzheimer's disease. This trial will be starting later this year and will likely be the pivotal trial that will help us decide if we are on the right path regarding early treatment. Needless to say, without the generous help of our many subject volunteers, we would not have come this far.

**Advances in technology in the past few years have brought about a number of apps and online tools for the smartphone, the tablet and the laptop to make life a bit easier for caregivers of people with dementia. These range from GPS devices to help relatives track a wandering family member, "pillbox" program apps to manage medications and appointments, and online 'message boards' for caregivers who can't find the time for conventional support groups. What are your views on the pros and cons of these technology-assisted devices?**

## DR. RENTZ:

I am an avid believer in using this new technology for assisting caregivers and patients. I have often advised my clinical patients to avail themselves of this technology, as these devices may keep people more independent longer. However, it is important for caregivers to monitor when these devices are no longer working.

I have also been actively involved in using iPad technology for administering cognitive tests. It is my hope that as individuals acquire these devices, subjects will not have to travel into the clinic to do cognitive testing, but can do them in the comfort of their own home. We are living in exciting times and I am glad that I can be a part of this new world.

**Lastly, tell us your hopes and goals for the role of neuropsychologists in the multidisciplinary team approach in caring for people affected by dementia?**

## DR. RENTZ:

Neuropsychologists have long had a vital role in the multidisciplinary team approach to the diagnosis and treatment of dementia. Despite how advanced we become with imaging technology, neuropsychological testing is still the gold standard for the diagnosis of dementia. Also, there is no substitution for good clinical care. A neuropsychologist can assist with the detection of early cognitive changes vs. normal aging, disease severity and speed of progression. They are vitally important for determining when a patient can still function independently or requires greater supervision. All of these factors are important to families for future planning purposes. Therefore, it is my opinion that any well-functioning dementia team will always value a neuropsychologist's input and participation.

**Thank you so much for your time, Dr. Rentz.**

# Talented Young Investigators at the Forefront of Research

## Marta Marquie-Sayagues, MD

**I AM FROM** Barcelona, Spain. I received my medical school training at the University of Barcelona, and completed my residency in Neurology at the Hospital de Sant Pau in Barcelona. I came to work at MGH as a research fellow in June 2010.

I decided to come to the MGH because it is a world-renowned center involved in cutting-edge research in

the field of functional neuroimaging, which is the topic of my doctoral thesis.

In 2010 I started working with the research team led by Dr. John H. Growdon in the Movement Disorders Unit, where I was involved in several projects related to neuroimaging in Lewy body disorders. We studied patients with Parkinson disease with and without dementia with a

new brain PET scan with the compound Altropine. Altropine is a marker of a neurotransmitter called dopamine, which is decreased in Parkinson disease. We found that the levels of dopamine in different areas of the brain relate to cognitive impairment in patients with Parkinson disease.

In 2012 I moved to the MassGeneral Institute for Neurodegenerative Disease, where I am now working with Dr. Teresa Gomez-Isla. Here I started a lab project with brain tissue samples from autopsies of patients with Alzheimer and Parkinson's diseases who had undergone a PET scan with the amyloid marker Pittsburgh compound B when alive. We intend to correlate the findings in the PET imaging with the pathological measurements of the amyloid protein in the brain tissue.



Dr. Marquie-Sayagues

My future career plans are to finish the projects I am involved in and to be able to publish our research findings. Then I would like to go back to Spain to present my thesis and get my PhD, and work in a Memory Disorders Clinic but also in research projects related to neuroimaging in dementia and movement disorders, with the knowledge acquired here at MGH.

Marta Marquie-Sayagues, MD

## Shuko Takeda, MD, PhD

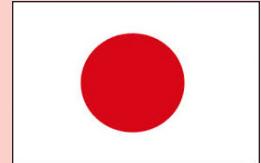
**Could you please tell us where you're from; when you came to MGH; how did you hear about us, and what made you choose to come here?**

I was born and raised in Japan, where I was awarded an MD degree from Hokkaido University. I then did my clinical training and in 2010 received a PhD from Osaka University,

where I began basic research on Alzheimer's disease. After serving as a project assistant professor at the University of Tokyo, I came to MGH in 2011 in order to expand my research career in the field of Alzheimer's research.

**What research projects had you been working on at MGH, and who is your mentor?**

With Dr. Brad Hyman's guidance, my research project is now focused on the metabolism of disease-related proteins in the brains of Alzheimer's disease. Some toxic proteins have been known to accumulate, aggregate and propagate between neurons in diseased brains. It is essential to understand how these pathological events progress during the development of Alzheimer's disease in order to produce effective therapies.



Dr. Takeda

**Tell us some interesting research findings (in non-scientific, layman terms) you've found? What made you choose this research topic?**

Recently, we established a novel technique that makes it possible to collect Alzheimer's-related proteins from the brains of freely-moving animals, which is called "in vivo microdialysis." Most previous studies of these disease-related proteins were either in vitro, such as neuron culture experiments, or post mortem. Instead, we are now studying these toxic proteins in awake, freely moving animal models; this provides us with valuable information about the disease progression. Combined with a well-established imaging technique in Hyman's lab, this unique system enables us to see disease processes in real time.

**Where are you heading off to after your time at the MGH, and your hopes for your future career plans that you can share.**

Japan is the most aging country in the world, and dementia is rapidly becoming a major health-care challenge. As a scientist and a physician, I want to tackle this disease from using both scientific and practical approaches. At MGH I have had the great fortune of working with a wonderful mentor, Dr. Hyman, who is my role model and inspires me to conduct high-quality basic research as well as clinical research. In the future, I want to be an independent "physician-scientist" who bridges the gap between lab discoveries and patient care.

Shuko Takeda, MD, PhD

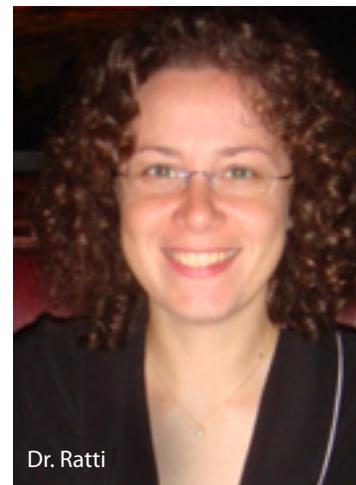
## Elena Ratti, MD

**MY NAME IS ELENA RATTI** and I grew up in Verona, Italy. Throughout my medical training and career I have always been interested in neurodegenerative diseases; indeed when I completed medical school in Italy my thesis project was on studying familial Parkinson's disease. I moved to US in 2006 to gain research experience at Duke University in Durham, NC, where I investigated molecular mechanisms of Alzheimer's disease involving the known disease risk factor ApoE. From there, I attended Emory University in Atlanta, GA for my Neurology Residency that I finished in July 2012. I then had the fortune to move to Boston to start a Clinical Research Fellowship in Amyotrophic Lateral Sclerosis (ALS) and Neurodegenerative Diseases within the Neurology Department at MGH. Through gaining experience as an academic ALS and Neurodegenerative disease clinical investigator, my ambition is to efficiently



bridge novel basic science research breakthrough discoveries into clinical practice in this field.

At MGH, I have the privilege to have Dr. Merit Cudkowicz as my mentor. She is not only a world renowned expert and a distinguished clinical investigator in neurodegenerative diseases and ALS, but also a unique mentor who has trained numerous successful clinical research scientists. I chose to pursue training at MGH in light of her distinguished academic achievements and



Dr. Ratti

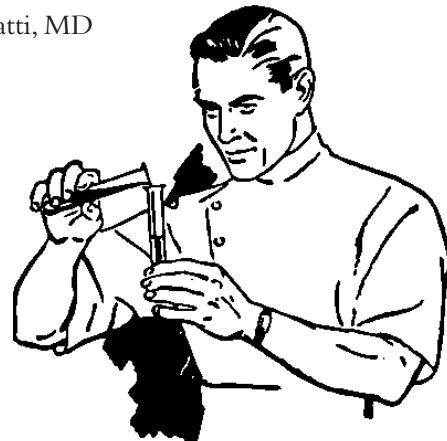
expertise in my areas of interest; the excellent training program in clinical research and the innumerable opportunities for fruitful collaborations in a range of disciplines at MGH.

I am particularly intrigued by the overlap of two clinically heterogeneous neurodegenerative diseases namely ALS and

Frontotemporal Dementia (FTD). Therefore my project is focused on achieving an improved understanding of FTD-ALS with the belief that by building on recent discoveries, I might contribute to an improved understanding of the shared mechanisms of neurodegeneration in these debilitating conditions and thereby disclose new potential biomarkers and/or novel targets for therapeutic intervention.

As for the future, I know that it will involve my passion, as a physician and clinical investigator, to make a beneficial impact on patients with neurodegenerative diseases where there is such tremendous unmet need and suffering from these destructive conditions.

Elena Ratti, MD



# Some Thoughts from Our Participants

**SIX YEARS AGO,** I heard Dr. Bradley Hyman's presentation on the important research that the MGH, Brigham and Women's, and Harvard Medical School were conducting on Alzheimer's disease and cognitive impairment. I was intrigued and asked him if there were some way that I might help and participate as a "data point" in these studies. At his suggestion, I signed up for his study, and in the past six years I have taken several memory/cognitive tests, given samples of spinal fluid and blood, and had some MRI's performed. Recently I participated in interesting vision and olfactory tests.

I have also decided to donate my brain to the Program, and have executed all the necessary paperwork for MGH to receive my brain for further study, after death. I continue to enjoy the personal challenges in taking these tests, have learned a great deal about this area of medicine, and have thoroughly enjoyed meeting so many interesting and dedicated professionals.

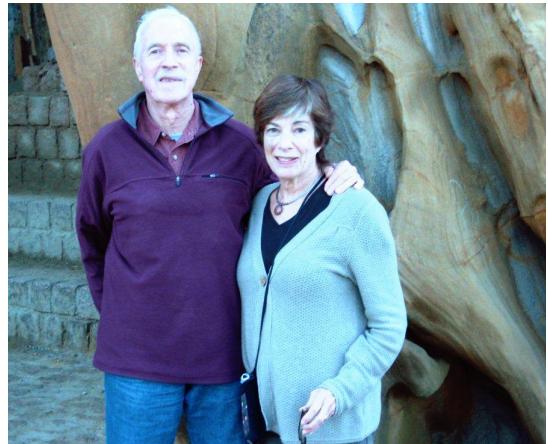
I have seen firsthand the effects of this terrible disease in my mother-in-law and several close friends, and by participating in these studies I feel that I am helping in some minuscule way to assist in finding a cure for dementia and Alzheimer's.

Thank you all so much for this opportunity.

Phil Schaffer

July 9, 2013

Lexington, MA



Phil and Fern Schaffer

**AM WRITING** to express my absolute delight and fascination with the new testing with which your organization is experimenting. Namely, the computer analysis of a subject's eye movements while viewing random objectives on a computer screen.

I found the testing to be quite simple, but am convinced that you're on to something that will become a scientific breakthrough in the study of Alzheimer's disease and memory loss in general. In my excitement over participation in this test, I have talked to a number of individuals who share my conviction of its potential value.

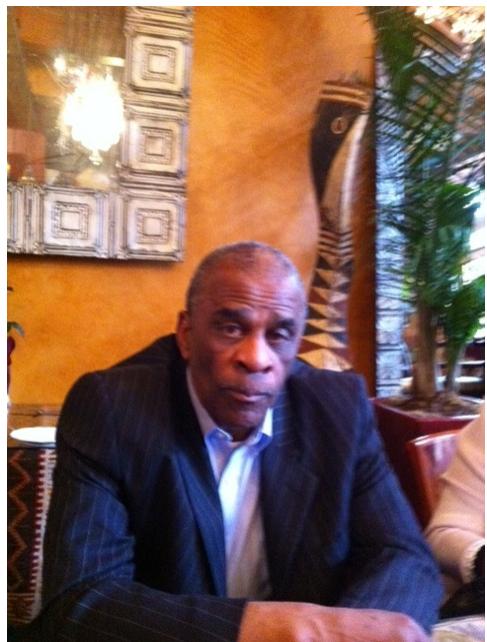
In addition, I want to thank you and your staff for the courtesies extended to me during my participation in the gerontology studies. The high level of professionalism, along with the personal engagement, have made me quite comfortable with the program.

I wish you continued success and look forward to my next visit.

Jackson Brookins

May 19, 2013

W. Peabody, MA



Jackson Brookins

## Greetings from the Clinical Coordinator

### To all our Memory Study participants:

*"Never doubt that a small group of thoughtful, committed citizens can change the world.*

*Indeed, it is the only thing that ever has."*

Whenever I see you here year after year for your research study visit, whenever you agree to do new tasks or repeat ones you've done before, whenever I hear that many of you have signed provisional consent for brain donation ... I think of this Margaret Mead quote. Indeed, it is you who will help to one day change the impact of neurodegenerative diseases.

We are trying to find ways to detect changes in the brain very early on. And we're trying many approaches. That's why we ask you to do different kinds of paper-and-pencil tests, to give us blood samples and cerebrospinal fluid samples, and to try new tests like the "smell test" and the eye tracking task. We've asked some of you to participate in affiliated studies at our center that involve MRI and PET scans. And we've told you about other studies that our colleagues in the area are doing. Our goal is to see if one or more of these approaches will help us detect early changes, even before symptoms occur. This is all in the research phase and that's why your participation and help is so valuable to us. We're working toward this goal together!

We were saddened that some of our subjects have recently passed away. We learned much from their time with us. Some of them had told their families that they wished to donate their brains to our research study ... so they're continuing to teach us things even now.

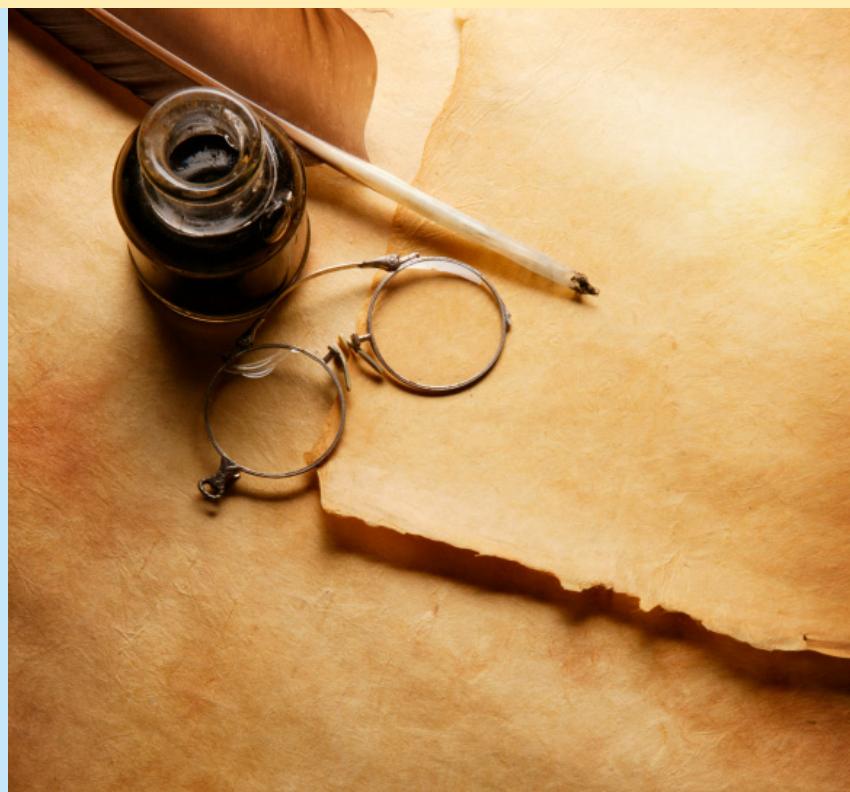
I always look forward to writing this little piece for the newsletter. It gives me a chance to express our appreciation for all that you do for us. You are a group of thoughtful, committed people who donate your time and energy to our work ... and make it so pleasant along the way!

Jeanette Gunther, MS

Clinical Coordinator

### Announcing A Centralized Telephone Number For Inquiries About Our Studies!

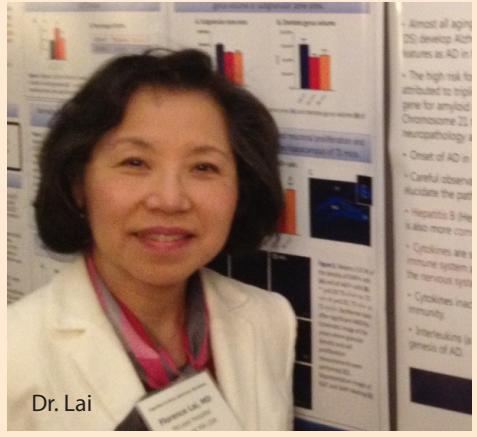
Interested in learning more about research studies and how you can get involved? Patients, caregivers, family members, and healthy volunteers can call **Sehily Jaimes at 617-643-5200** to learn about all of the exciting research opportunities we have going on at the MADRC!



# Adults with Down Syndrome Very Prone to Develop Alzheimer Disease

by Florence Lai, MD

**JIM WAS VERY EAGER** to participate in the NIH-funded Multicenter Vitamin E Trial in Aging Persons with Down syndrome and was “Numero Uno” when the study finally started at McLean Hospital, affiliate of MGH. As one of more than 700 similar adults whom I had evaluated over the years, he was very likely to develop Alzheimer disease, so the first clinical trial of an antioxidant in almost 350 individuals with Down syndrome from 21 international sites was an important milestone.



Dr. Lai

The brain changes of Alzheimer disease (AD) occur in virtually all adults with Down syndrome (DS) over the age of 35–40 years of age, but the clinical dementia was harder to diagnose due to the presence of intellectual disability. Those with higher levels of functioning show similar declines in memory, language, learning, spatial and temporal orientation, mobility, personality and activities of daily living as those with AD in the general population. From serial evaluations, it is now known that the average onset of the dementia in those with DS is in the early 50s with a range from 40 to the late 60s. Duration is 5–6 years on average, with some surviving for more than a decade. Although the incidence of dementia is not 100 percent, estimates vary from 30 percent to about 50 percent in those between 50–59 years of age with higher percentages after that.



Image courtesy of princeeven.net

Individuals with DS have three copies of chromosome 21, and in 1987 published reports including one from MGH, implicated the gene for the precursor of beta-amyloid protein (located on Chromosome 21), as being associated with death of specific brain cells leading to Alzheimer disease. With 3 copies of this gene, adults with DS are predisposed to this deadly disease.

There is mounting interest in studying persons with Down syndrome as this population may hold the key to unlocking our understanding of Alzheimer disease. In April 2013, over 100 researchers, practitioners and research-oriented family members gathered near Washington DC for three days of intensive presentations on genetics, mouse models, pathology and clinical aspects of Down syndrome.

My own previous studies on the effect of Apolipoprotein E genotype on AD in DS mirrored that in the general population with AD. A recent analysis of my patients with DS seems to implicate aspects of the immune system in the genesis of AD.

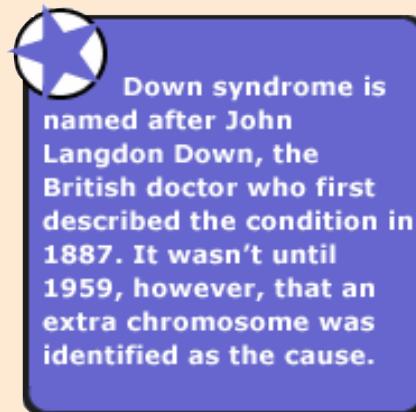


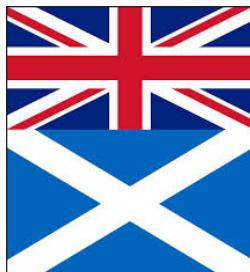
Image courtesy of KidsHealth.org

Jim was a real pioneer in DS research. He not only participated in clinical research, but his family donated his brain for neuropathological and neurochemical studies upon his death. Although the Vitamin E study yielded negative results, the infrastructure is now available for future studies. With time, energy and funding, we can find the factors that exacerbate or ameliorate the onset and progression of AD, and perhaps even find a cure for this devastating condition. I know that all my patients with DS and Jim in particular with his ever-smiling face would have said, “Go for it. Do it!” ♦

## Bon Voyage to Three Superb Trainees

### Tara L. Spires-Jones, DPhil

I AM ORIGINALLY from Leander, Texas but came to MGH from the University of Oxford in England where I did my doctoral work. While I was at Oxford, I came to give a research talk at MIND in Dr Young's "flying pigs" lab meeting. Everyone I met in the department was amazing. In particular, talking with Prof Brad Hyman about his ideas surrounding degeneration in Alzheimer's disease and how they overlapped with my studies in the Huntington's field drew me to the department for a postdoctoral project. I came for a postdoc in 2004, fully



Flags of the United Kingdom and Scotland



Dr. Spires-Jones and family

expecting to move on in a couple of years, but the research environment and mentoring from Prof Hyman were so wonderful that I'm still here almost 10 years later running my own lab as an assistant professor.

My group studies the degeneration of the brain during Alzheimer's disease. Memory is made possible by the ability of synapses, the connections between neurons in the brain, to change in response to environmental inputs. In Alzheimer's disease, memory declines because synapses and neurons become dysfunctional and die. In fact, loss of synapses very strongly corresponds to the severity of dementia in Alzheimer's patients. The goal of my work is to find out whether the two key disease-causing proteins in Alzheimer's – amyloid beta and tau – act together to cause this synaptic degeneration. Further, we test therapeutic treatments in disease models to move toward drug

treatments to benefit patients. We have applied a new cutting-edge imaging technique to brain tissue from our generous patient donors to study the problem of synapse degeneration in Alzheimer's. With this technique called array tomography, we recently discovered that the Apolipoprotein E4 gene, which increases the risk of developing Alzheimer's, causes more toxic Abeta to be transported to synapses. This is an important link between the strongest genetic risk factor for sporadic Alzheimer's disease (apolipoprotein E4) and synapse loss, which is the strongest correlate of dementia in the disease process.

Going forward, I am moving back to the United Kingdom to continue my work on Alzheimer's disease. As of this summer, I will be a Reader and Chancellor's Fellow at the University of Edinburgh where I am building a new lab and have started collecting human tissue for array tomography from patient donors to the Edinburgh Brain Bank. Prof Hyman and I will continue our fruitful collaborations examining both models of the disease and human brain tissue to move toward effective treatments to prevent or reverse dementia in Alzheimer's disease.

Tara L. Spires-Jones, DPhil

### Alberto Serrano-Pozo, MD, PhD

I WAS BORN IN MÁLAGA, in the South coast of Spain, where I got my MD degree. After finishing my Neurology residency and a clinical and research fellowship on dementias in



Seville, I joined MIND in July 2008. During my training in Spain I soon became aware of the huge medical and social challenge that Alzheimer disease represents and decided to devote my career to help to find a cure. When Dr. Bradley Hyman and Dr. John Growdon accepted to mentor me, I felt a dream had become true.

Over these almost five years, I have been working both at the lab and at the Gerontology Research Unit (GRU). At the GRU, I have had the great honor to be part of the staff of the longitudinal cohort study and interact with wonderful colleagues and many of our lovely subjects. At the lab, I have been very fortunate to work with the Massachusetts ADRC brain bank. I have studied the brain of patients who died with Alzheimer disease using quantitative histological methods. Specifically, I have quantified the amyloid plaques and the

neurofibrillary tangles that deposit in the brain cortex in Alzheimer disease, as well as the glial (non neuronal) cells that are known to react to plaques and tangles. Among other observations, these studies have revealed that tangles and glial responses accumulate over the clinical course of the disease, whereas the extent of amyloid plaque deposition does not track well with disease progression because amyloid deposition occurs for the most part before symptom onset. These findings have important implications in the development of



Dr. Serrano-Pozo

imaging biomarkers for the progression of Alzheimer disease. In addition, using similar methods, I have characterized the brains of five Alzheimer patients who had enrolled in an anti-amyloid immunization (vaccine) clinical trial when they were at the mild-to-moderate phase of the disease. I compared them with the brain of 13

Alzheimer patients with similar disease severity and of 8 elderly subjects with normal cognition from our brain bank, and found that vaccine-treated patients had not only fewer plaques but also some subtler findings suggesting a beneficial effect on neurons, such as an improvement in the trajectory of neuron axons (typically more tortuous in the brain with Alzheimer disease), and some amelioration of tangles. These findings have encouraged the testing of anti-amyloid immunization strategies in clinical trials at an earlier stage of the disease.

I will always remember these five years as one of the best experiences in my life and will always feel in debt with my mentors and the Massachusetts ADRC team. The generosity and motivation of my subjects and my colleagues at the GRU and at the lab are the best lessons that I am taking with me. During the next 4 years I can be found doing my US Neurology residency at University of Iowa Hospitals & Clinics. To pursue my goal of a clinician-scientist career, my next necessary step will be to become a Board-certified neurologist in the US.

Alberto Serrano-Pozo, MD, PhD

## My 'American Scientific Dream' Alvaro Sanchez-Ferro, MD

I AM A NEUROLOGIST from Madrid (Spain) and we have a special interest in the research of two of the most common illnesses related to aging i.e. Alzheimer's and Parkinson's disease.



As part of my current fellowship program, I was granted the opportunity of visiting any leading research institution across the world. I decided to join the MGH Alzheimer Disease Research Center (MADRC) under the mentorship of Dr. Brad D. Hyman and Dr. Gomez-Isla for eight months. I chose this center because of the projects in which I had the opportunity to be involved and the possibility of working with these first-class scientists.



Dr. Sanchez-Ferro

My main contributions were related to a new tool aimed to detect Alzheimer's disease before it produces symptoms (called Eye Tracking) and which we are still evaluating. Additionally, I collaborated on other related group projects to explain the mechanisms that permit some people to be more resilient to Alzheimer's disease.

I consider that this experience has been beyond my expectations, which were really high. Not only had I the opportunity of being involved in research that might directly help to find solutions for the affected individuals, but also I had the possibility of exposing myself to the most dynamic, flexible and tenacious scientific environment I had ever known.

After this wonderful and enriching episode, I will start a new program with the Massachusetts Institute of Technology. It aims to develop new imaging tools to solve unmet needs in biomedicine. My dream will be to contribute directly to improve the quality of care for people affected by those diseases and what I am sure of is that this period at the MADRC will help to make my dream come true.

Alvaro Sanchez-Ferro, MD

# We're Currently Recruiting!

STUDY TITLE	WE'RE LOOKING FOR	BRIEF STUDY DESCRIPTION
Dominantly-Inherited Alzheimer Network (DIAN)	Adults (age 18 + ) with a biological parent who has Dominantly-Inherited Alzheimer's Disease (DIAD)	The purpose of the study is to try to understand the changes that occur in patients with genetic mutations causing DIAD over time. The DIAN research volunteers are members of families in which AD is dominantly-inherited, meaning that about 50 percent of the individuals in each generation of a family develop AD, generally before age 60. Over time, participants will have MRIs, PET scans, Lumbar Punctures, and memory testing.
Evolution of Memory-Related fMRI Activation Over the Course of MCI and AD	Healthy adults (age 65-90) and adults with MCI and mild AD dementia (age 55-90)	The purpose of this research study is to find out if functional MRI images of the brain can be used to diagnose and monitor the course and treatment of Mild Cognitive Impairment (MCI) and AD (Mild Alzheimer's Disease). Subjects must have a study partner and be willing to come for six to eight clinic and imaging visits over the course of two to three years.
Implications of Amyloid Deposition in Clinically-Normal Older Individuals	Healthy adults, age 60 - 90	The purpose of the study is to develop ways for understanding memory changes that occur with age. Participants will be asked questions about their memory and must have a friend or relative who can answer questions over the telephone about the participant's day-to-day activities.
The Harvard Aging Brain Study (HABS)	Healthy Adults, age 50 - 90	The purpose of the study is to find out whether the changes that a doctor sometimes sees on a brain scan are related to early memory changes that occur in older healthy adults. It will take about 5 years to complete the study. During this time, you will be asked to have 4 MRI scans, 2 PIB-PET scans, 2 FDG-PET scans, 5 fasting blood draws, and up to 7 sessions of thinking and memory testing, for a maximum of 17 study visits. You may also participate in an optional sub-study where you will have 2 lumbar punctures ('spinal tap').
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and the Effect of BMS-241027 on Cerebrospinal Fluid Biomarkers in Subjects with Mild Alzheimer's Disease	Adults with Mild AD, 50-90	4 month clinical trial to evaluate the efficacy, safety and tolerability of BMS241027 in reducing abnormally high levels of a protein called tau that is found in Alzheimer's Disease (AD). We are looking for participants between the age of 50 and 90 who are in stable medical condition with a reliable study partner able to accompany them to study visits. Must have been diagnosed with mild AD and be willing to undergo MRI scans and lumbar puncture. Parking is compensated.
A Randomized, 18-Week, Placebo-Controlled, Double-Blind, Parallel-Group Study of the Safety and Efficacy of PF-05212377 (SAM-760) in Subjects with Mild to Moderate AD with Existing Neuropsychiatric Symptoms on a Stable Daily Dose of Donepezil	Adults with AD, age 60 and older	22 week clinical trial to evaluate the efficacy and safety of PF-05212377 (SAM-760) to improve cognition and decrease some behavioral symptoms associated with Alzheimer's Disease (AD). We are looking for participants ages 60 and older who are in stable medical condition, on a stable dose of Aricept (donepezil), and with a reliable study partner able to accompany them to study visits. Must have a diagnosis of Alzheimer's Disease. Compensation is provided for participation.
A Placebo-Controlled, Double-Blind, Parallel-Group, Bayesian Adaptive Randomization Design and Dose Regimen-Finding Study to Evaluate Safety, Tolerability, and Efficacy of BAN2401 in Subjects with Early Alzheimer's Disease (BAN2401-G000-201)	Adults with AD, age 50 - 90	79 week clinical trial to evaluate the efficacy and safety of BAN2401 in reducing abnormally high levels of a protein called amyloid that is found in Alzheimer's Disease (AD). We are looking for participants between the age of 50 and 90 in stable medical condition and with a reliable study partner able to accompany them to visits. Must have been diagnosed with Mild Cognitive Impairment (MCI) or mild AD and are willing to undergo MRI and PET scans. Compensation is provided for participation.
Disentangling the Contribution of Tau to Aging, Dementia, and Neurodegeneration	Healthy Adults and adults with AD, MCI, CTE, and FTD, age 20-90	The purpose of this study is to determine the presence of the protein Tau in the brain in a variety of populations, ranging from healthy adults to those diagnosed with a neurodegenerative disease. It will take up to 6 visits to complete this study. Over the course of these visits, you will be asked to have 1 MRI scan, 1 T807 PET scan, 1 PIB PET scan, 1 fasting blood draw, and 2 cognitive testing sessions. You may also participate in an optional sub-study for lumbar puncture.

Interested? Contact our Outreach & Recruitment Coordinator, Sehily Jaimes, at 617-643-5200

# ANNOUNCING OUR SPANISH WEB- PAGES!

**OUR MAIN WEB-PAGES** are now available in Spanish – check them out at [www.madrc.org](http://www.madrc.org). We hope that these pages will extend our reach to the large Spanish-speaking communities interested in our work!

Mucha gracias to the dedicated team from Teresa Gomez-Isla, MD, PhD's lab who had made it all possible:

Isabel Barroeta-Espar, MD

Beatriz Gomez Perez-Nievas, PhD

Marta Marquie-Sayagues, MD

Alvaro Sanchez-Ferro, MD



*El Jaleo* by John Singer Sargent



*Ball in Columbia* by Fernando Botero

Courtesy of the Isabella Stewart Gardner Museum of Art

Courtesy of the New York Metropolitan Museum of Art

Courtesy of Carlexonline.com



Can you identify the flags of these countries?

# E-Letter From Across the Border

by Liang Yap, PhD



**EACH YEAR**, we receive our fair share of correspondence from research collaborators and friends from across the globe, but nothing pleases us more than when young people write to tell us that they are interested to learn more about what we do. Several months ago, our Center Director, Dr. Hyman, received an email from students of the American School Foundation of Guadalajara, Mexico, indicating that they were working on a high school science project on Alzheimer's disease, and wondered if they could interview one of our staff members. Dr John Growdon – our Founding Director responded, and was glad to be of some help.

We are here to serve our research participants, patients and their loved ones, and we are thrilled when we can instill our passion for the neurosciences in our future generations. ♦



Manuel Ney and Marcus Moix



Min Woo, Alma Sofia Vazquez and Manuel Ney

From: Marcus Moix [mailto:[marcus.moix@asfg.edu.mx](mailto:marcus.moix@asfg.edu.mx)]

Sent: Tuesday, November 13, 2012 12:31 PM

To: Yap, Liang, Ph.D.

Subject: Fwd: Interview about Alzheimers

Dear Dr. Liang

We thank you for the support and we would love to send Dr. Hyman the questions we have, but we were hoping to schedule an interview with any available doctor any day of this week. If possible, the best time for an interview for us would be from 12:00 to 12:20 or anytime after 2:30. We know that you are very busy people and we thank you so much for your time.

These are the questions from Dr. Hyman and they are also the ones we will be asking

- 2.What are some of the things you advise your patients to do that might slow the onset of symptoms?
3. Can early detection have a patient from alzheimers?
8. To what extent can we prevent Alzheimer's disease?
11. What part does genetics play in the acquiring of alzheimer?
12. Why does age increase the chances of getting alzheimer?

Thanks for you help and time

Marcus Moix

From: Marcus Moix [mailto:[marcus.moix@asfg.edu.mx](mailto:marcus.moix@asfg.edu.mx)]

Sent: Thursday, November 08, 2012 12:10 PM

To: Hyman, Bradley T., M.D.

Subject: Interview about Alzheimers

Dear Dr. Hyman

My name is Marcus Moix and I am writing on behalf of Manuel Ney, Min Woo and Alma Sofia Vazquez. We are all students at the American School Foundation of Guadalajara, Mexico. Currently, we are investigating the question, "To what extent can we prevent Alzheimer's Disease?" as part of a high school science project. While searching for Alzheimer's Disease research, we came across your contact information for Massachusetts Alzheimer's Disease Center and noticed that you are the center's director. We hope that you would be willing to conduct a recorded interview with us at your convenience or provide information as to who could help us. Please let us know if you would be available, and we will schedule an interview in subsequent emails.

Thank you for your time and consideration of our request,

Marcus Moix, Manuel Ney, Min Woo and Alma Sofia Vazquez



# Keep in MiND!

A NEWSLETTER FOR FRIENDS AND SUPPORTERS  
OF THE MASSACHUSETTS ALZHEIMER'S DISEASE  
RESEARCH CENTER AND THE MEMORY STUDY

[www.madrc.org](http://www.madrc.org)

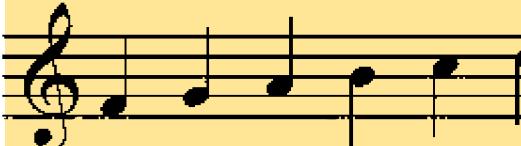
## LAST NOTES...

### Keeping Our Fingers Crossed!

by Liang Yap, PhD

**DID OUR READERS** ever wonder what ever happened to our Spring/Summer 2013 issue of our newsletter? Got lost in the snail-mail, perhaps? Well ... not quite. All of us were kept on our toes as we raced towards meeting the June 11, 2013 deadline to submit our 5-year grant renewal application to the National Institute on Aging (NIA), so much so that when we finally had a chance to 'come up for air', summer had already arrived in our backyard!

We sure hope all our hard work will pay off when grant funding results are announced in the Spring 2014. Till next time ... stay 'TUNED', and keep your fingers crossed for us!



**ARE YOU INTERESTED** to sponsor one or more international medical students to learn more about the exciting world of neuroscience in our research labs next summer? Your support could help pay for their travel and lodging expenses!

Questions? Please contact Shawn Fitzgibbons, Senior Director of Development, at 617-643-0447 or [sfitzgibbons@partners.org](mailto:sfitzgibbons@partners.org)

