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Press Room, Nov. 9–13: (619) 525-6260

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**OUR RELATIONSHIP WITH FOOD: WHAT DRIVES US TO EAT AND NEW INSIGHTS INTO
EATING DISORDERS**

*New Treatments for Binge Eating, How Our Diet Impacts Brain Function, and the Connection Between Marijuana
and Obesity*

SAN DIEGO — A growing body of evidence shows the impact of diet on brain function, and identifies patterns of brain activity associated with eating disorders such as binge eating and purging. The findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Millions of people worldwide suffer from eating disorders such as anorexia, bulimia, and binge eating. With increased risk for psychiatric and chronic diseases, today's studies are valuable in helping generate new strategies to treat disorders from obesity to anorexia.

Today's new findings show that:

- Targeted magnetic stimulation of the brain reduces the symptoms of severe eating disorders, including bingeing and purging. These findings may represent a new treatment tool for patients with eating disorders (Jonathan Downar, MD, PhD, abstract 540.01, see attached summary).
- Rats that are more naturally impulsive tend to consume more calories on a binge. Findings suggest that this may be due to an imbalance in the brain's serotonin system (Noelle Anastasio, PhD, abstract 547.13, see attached summary).

Other recent findings discussed show that:

- Consuming a diet of red meat and processed foods is linked to a decline in verbal memory in the elderly after just 36 months (Samantha Gardener, see attached summary).
- Consuming cannabis can influence body weight of offspring for generations (Yasmin Hurd, PhD, presentation 685.05, see attached speaker summary).
- Eating a sweet, high-fat meal sets off a series of events that includes the release of insulin and suppression of dopamine, leading to less interest in food-related cues in the environment (Stephanie Borgland, PhD, presentation 685.06, see attached speaker summary).

“As scientists uncover the impacts of diet on brain function, the adage ‘You are what you eat,’ takes on new meaning,” said press conference moderator Fernando Gomez-Pinilla, PhD, of the University of California, Los Angeles, an expert in the impact of the environment on brain health. “We cannot separate the nutritional benefits of food for the body from that of the mind. What we put into the body also shapes the brain, for better or for worse.”

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find more information on the impact of diet on the brain at BrainFacts.org.

Related Neuroscience 2013 Presentations:

Minisymposium: **Neuroimaging Guided Cognitive Regulation of Food Stimuli: Implications for Obesity**
Monday, Nov. 11, 1:30–4 p.m., Room 28A

Minisymposium: **Food for Thought: Experiential, Hormonal, and Neural Antecedents of Obesity**
Wednesday, Nov. 13, 8:30–11 a.m., Room 6E

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Abstract 540.01 Summary

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Brain Stimulation Therapy Helps Control Patients' Binge Eating and Purging in Pilot Study

*Noninvasive treatment changes brain activity in ways that improve symptom control;
brain imaging predicts patient's response to treatment*

Magnetic stimulation of specific areas of the brain appears to help certain patients with severe eating disorders involving bingeing and purging of food, according a new study. Symptoms improved by more than 50 percent in nearly half of study participants, and a third of the cases showed an 80-100 percent reduction after treatment. This research was presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The new study, led by Jonathan Downar, MD, PhD, and Blake Woodside, MD, of the University of Toronto, also used brain imaging to identify differences in brain activity between those patients who improved dramatically and those who showed little or no improvement.

"Eating disorders such as anorexia and bulimia affect more than 8 million people in North America," Downar said. "They can also be deadly: up to one in five people with anorexia die prematurely from medical complications. Our existing treatments are ineffective for many patients. New, more effective treatments are urgently needed."

In the study, researchers applied repetitive transcranial magnetic stimulation (rTMS), an emerging therapy that uses powerful, focused magnetic field pulses to stimulate target brain regions non-invasively. They gave 20 patients 20 sessions of a novel form of rTMS, directing it toward a part of the frontal lobes called the dorsomedial prefrontal cortex – a different brain area from the usual target of conventional rTMS. This part of the brain is considered important for self-control of thoughts, emotions, and behavior, a function that is often impaired in patients with eating disorders.

Enhancing activity in this part of the brain appeared to help patients control their urges to binge and purge, and also relieved symptoms of depression and anxiety. Brain imaging then revealed that a patient's response to treatment could be predicted by differences in brain activity in regions that respond to rewards and regions involved in impulse control. Patients who responded to treatment also showed specific types of changes in brain activity in regions associated with goal-directed decision-making over the course of the rTMS treatment. These changes may illustrate the mechanism by which rTMS helps patients to control impulses and make alternative decisions when faced with an impulse to binge or purge.

"Our study suggests that rTMS could be a new and highly effective form of treatment for certain types of patients with eating disorders. The brain imaging results also suggest that we may be able to identify these individuals based on the patterns we see in their brain activity," Downar said. "By using brain imaging to detect these patterns, we may eventually be able to predict which patients are most likely to benefit from rTMS after other treatments have failed."

This research was supported with funds from The Toronto General and Western Hospital Foundation and the Klarman Family Foundation.

Scientific Presentation: Tuesday, Nov. 12, 8–9 a.m., Halls B–H

540.01, Baseline and change resting-state functional correlates of rTMS of the DMPFC for medically refractory anorexia and bulimia nervosa
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TECHNICAL ABSTRACT: Transcranial magnetic stimulation (rTMS) has been recently suggested as a potential treatment for anorexia and bulimia nervosa. Previous research has shown modest efficacy with rTMS for eating disorders using the conventional dorsolateral prefrontal cortex target. However, recent neuroimaging research suggests that the dorsomedial prefrontal cortex (DMPFC) is a key region for impulse control and behavior regulation, including bingeing and purging behavior. Thus, the DMPFC may be a potential rTMS target for the treatment of eating disorders.

20 patients with treatment refractory anorexia and bulimia nervosa underwent 20 sessions of open-label, add-on rTMS to the DMPFC (10 Hz bilateral stimulation, 120% resting motor threshold). Clinical measures, structural and resting-state scans were obtained before and after treatment. Analysis was performed in FSL. Data was first pre-processed (motion corrected, spatially smoothed, regression of global, white matter and cerebrospinal signal, bandpass filtered). Following pre-processing seed-based resting state analysis was performed for a priori regions-of-interest (bilateral ventral striatum [BVS] and subgenual cortex [sgACC]) and a region in proximity to the area stimulated (DMPFC). Purges/week change (baseline-week 4) categorized subjects into a responder (improvement over 50%) or a non-responder (improvement under 50%). This was used as a regressor for the following group-level analysis: 1) baseline connectivity, and 2) connectivity change.

Clinical results showed that purging from baseline to week 4 improved from 25.3 ± 38.8 episodes/week to 17.3 ± 19.2 episodes/week. Baseline DMPFC connectivity was not significantly correlated to response. However, for the BVS seed, high pre-treatment functional connectivity to the precuneus and posterior cingulate cortex (PCC), and for the sgACC seed, high pre-treatment functional connectivity to the precuneus and PCC and low functional connectivity to the right hippocampus and amygdala and midbrain Raphé nuclei, were significantly correlated to clinical response. sgACC connectivity change was not significantly correlated to treatment response. It was found that decreased BVS connectivity to the precuneus and PCC and decreased DMPFC connectivity to the frontopolar cortex were significantly correlated to clinical response. In general, this preliminary study showed altered connectivity in midbrain serotonergic structures and corticostriatal and corticocortical pathways previously implicated in emotion regulation and in the pathophysiology of disordered eating behavior. A randomized control trial as a next step may be warranted.

Abstract 547.13 Summary

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Researchers Find Common Link Between Binge Eating and Impulsive Behavior

Rodent study suggests imbalance in the brain's serotonin system at the root of both

Some people may eat way past the point of fullness, and then eat some more. A new rodent study shows that an inherent level of impulsive behavior helps to determine the magnitude of binge eating — particularly of foods rich in sugar and fat. The findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The study, led by Noelle Anastasio, PhD, and Kathryn Cunningham, PhD, of the Center for Addiction Research at the University of Texas Medical Branch, demonstrates that both impulsive behavior and binge eating are modulated at a molecular level by the brain's serotonin system. It also sheds light on binge eating disorder (BED), which is linked to severe obesity and is the most prevalent eating disorder in the United States.

“Our research suggests that the use of medications to fine-tune the brain's serotonin system may allow us to correct problems associated with both impulsive behavior and uncontrolled eating,” Anastasio said.

Serotonin and its receptors on brain cells operate within an integrated network that spans different regions of the brain and orchestrates a balance between impulsive and goal-driven behaviors. Serotonin also modulates appetite. Impulsive behavior — action without sufficient foresight — has been noted before as one of several drivers of binge eating. But, until now, scientists' understanding of the molecular basis of this relationship has been limited.

To better understand this relationship, the researchers worked with two groups of rats — one group that was highly impulsive (HI rats), and the other group that had more self-control (low impulsive, or LI rats). Compared to LI rats, HI rats repeatedly binged on chow high in sugar and fat. In addition, the more impulsive the rat, the more calories it consumed during a two-hour binge period.

Furthermore, elimination of a crucial serotonin receptor, 5-HT_{2C}R, in one part of the brain (the nucleus accumbens) led to even more bingeing and greater impulsivity. This suggests that binge eating involves an imbalance in the brain serotonin system that controls both the ability to control impulsive behavior and the desire to binge.

This research was supported with funds from The Klarman Family Foundation, the National Institute on Drug Abuse, and the University of Texas Medical Branch Center for Addiction Research. Senior author Kathryn Cunningham, PhD, is a consultant to Arena Pharmaceuticals.

Scientific Presentation: Tuesday, Nov. 12, 8–9a.m., Halls B–H

547.13, Stop, put that cookie down: Impulsive action and binge intake of palatable food

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TECHNICAL ABSTRACT: Food intake is essential for survival, but maladaptive patterns of intake, possibly encoded by a pre-existing vulnerability coupled with the influence of environmental variables, can modify the reward value of food. Impulsivity, a predisposition toward rapid unplanned reactions to stimuli, is one of the multifaceted determinants underlying the etiology of dysregulated eating, its evolving pathogenesis, and treatment outcomes. Impulsivity and dysregulated eating converge mechanistically at the level of serotonin (5-HT) neurotransmission at the 5-HT_{2A} receptor (5-HT_{2A}R) and 5-HT_{2C}R within an integrated brain network (e.g., prefrontal cortex, nucleus accumbens), that orchestrates a balance between stimulus-driven and goal-driven behaviors. Disturbances in this system may engender maladaptive eating behaviors [esp., binge eating on palatable high fat/sugar (“sweet-fat”) foods] and the response to food stimuli seen in binge eating disorder. Yet, our understanding of the reciprocal relationships linking impulsivity to binge eating and/or relapse in the presence of food stimuli, and the shared neurobiological mechanisms, is very limited.

We developed a rat model of binge eating behavior in which “binge” rats allowed unrestricted 2-hr access to sweet-fat chow (17% sucrose and 45% fat by kCal) at the start of the dark cycle consume significantly greater calories relative to control rats maintained on brown chow or continual sweet-fat chow. The highly-

selective and efficacious 5-HT₂CR agonist WAY163909 suppresses binge intake of sweet-fat chow ($p < 0.05$) at doses lower than those required to suppress brown chow intake.

To explore the relationship between impulsivity and binge-eating, we identified high (HI) and low impulsive (LI) rats in a novel model of impulsive action (1-choice serial reaction time task) in which a sweet-fat food pellet was the reinforcer. HI rats repeatedly exhibited significantly higher bingeing on sweet-fat chow compared to LI rats ($p < 0.05$); a positive correlation was observed between levels of impulsivity and caloric intake during the binge ($r = 0.457$, $p < 0.05$). Elimination of the 5-HT₂CR in the nucleus accumbens resulted in high binge eating, high impulsivity, and a shift in functional tone of the homologous 5-HT₂AR. Thus, inherent impulsivity and binge eating reciprocally interact at the level of the 5-HT₂R to control behavior. Through addressing a fundamental gap in our knowledge of how the neural and behavioral aspects of impulsive action are related to binge eating, we hope to develop pharmacological strategies to minimize binge eating and enhance clinical practice for disorders of overeating.

Speaker Summary (89.01)

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Dietary Patterns and Their Association with Cognitive Decline: Data from the Australian Imaging, Biomarkers and Lifestyle Study of Aging

Saturday, Nov. 9, 1–2 p.m., Halls B–H

This research indicates that consuming larger quantities of foods included in a western dietary pattern is associated with greater cognitive decline in visuospatial functioning after 36 months. Foods included in the western dietary pattern are red and processed meats, high fat dairy products, chips, refined grains, potatoes, sweets and condiments.

In contrast, the Mediterranean diet, a healthy eating pattern is associated with less decline in executive function. Foods included in the Mediterranean diet are vegetables, fruits and fish.

We saw no effect on other areas of cognition, including verbal and visual memory, language and attention and any of the three dietary patterns. These associations were seen after controlling for the effect of known Alzheimer's disease risk factors including age, cardiovascular risk factors and presence of an Apolipoprotein ε4 allele which is the most common genetic risk factor for Alzheimer's disease.

The world's population is growing older due to improved healthcare and nutrition. As a result, Alzheimer's disease prevalence is rapidly increasing. Cognitive decline is the progressive loss of cognitive functions, including memory, and may lead to dementia, of which Alzheimer's disease is the most common type. The focus of the current research climate is shifting from understanding Alzheimer's disease pathology and diagnosis to primary prevention and intervention strategies. Diet represents one potential intervention strategy accessible to all.

There is increasing evidence that components in the foods we consume interact with each other to impart disease protection and a higher level of health. The evidence for health benefit appears stronger when foods are inserted into synergistic dietary patterns, rather than considered as individual foods or food constituents.

Our findings are in agreement with previously published work on dietary patterns and cognitive decline. In American populations, it has been shown that higher Mediterranean diet adherence is associated with lower Alzheimer's disease risk and slower cognitive decline. Higher consumption of a 'whole foods' pattern (similar to our prudent pattern) has been associated with less risk of cognitive deficits, and consumption of a 'processed foods' pattern (similar to our western pattern) has been associated with higher risk of cognitive deficits. Our results further highlight the importance of eating a healthy diet with respect to reducing risk for cognitive decline and Alzheimer's disease. To our knowledge, this is the first study extensively comparing Mediterranean diet, western diet and prudent diet scores to cognition, cognitive decline and change in clinical classification in an elderly, Australian cohort, to assess protective and detrimental effects of these diets.

The aim of our study was to investigate the association of three dietary patterns — Mediterranean diet, western diet and prudent diet — with cognitive change over three years, assessed using a comprehensive neuropsychological test battery. Dietary data was collected using food frequency questionnaires. Our results report on data from 527 men and women from a well-characterized, Australian elderly cohort, drawn from the larger Australian Imaging, Biomarkers and Lifestyle study of ageing.

Dietary patterns have not been tested extensively for their association with maintaining cognition or reducing cognitive decline. The number of published studies in this area is fairly limited, and consequently there is a need for further investigation in well-characterized ageing cohorts. It is hoped that the information generated can be used in the development of preventative strategies against cognitive decline and Alzheimer's disease.

This research was supported by national funding from the Edith Cowan University, the Commonwealth Scientific and Industrial Research Organisation the Mental Health Research Institute, Alzheimer's Australia, National Ageing Research Institute, Austin Health, CogState Ltd., Hollywood Private Hospital, Sir Charles Gairdner Hospital, the National Health and Medical Research Council, the Dementia Collaborative Research Centres program, The McCusker Alzheimer's Research Foundation, and the Government of Victoria.

Speaker Summary (685.05)

Speaker: Yasmin Hurd, PhD
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Paternal Cannabis Exposure During Adolescence Reprograms Offspring Reward Neurocircuitry in a Sex-Dependent Manner

Minisymposium: *Food for Thought: Experiential, Hormonal, and Neural Antecedents of Obesity*
Wednesday, Nov. 13, 8:30–11 a.m., Room 6E

Obesity continues to be a major public health problem in the United States and is of growing concern in other Western societies. In recent years, questions related to the risk of obesity based on environmental factors have been of significant interest. Though environmental consequences during the course of one's own lifespan clearly impacts the development of obesity, there is also increasing evidence that these effects may have consequences for the health and development of subsequent generations of offspring.

One class of environmental triggers with potential for multi-generational impact is drugs abuse, such as cannabis. Similar to the association of paternal cigarette smoking with body mass index in male offspring in humans, another relationship seems to emerge with the consumption of cannabis. Cannabis mediates its effects through engagement of the endocannabinoid system, which is an important regulator of feeding and metabolism. Particularly relevant to trans-generational epigenetic transmission is the fact that in addition to the regulation of feeding and metabolism, the endocannabinoid system is well documented to be involved in DNA remodeling in the development of reproductive cells. It now evident from Yasmin Hurd and colleagues, of the Icahn School of Medicine at Mount Sinai in New York, that the main psychoactive component of cannabis, $\Delta 9$ -tetrahydrocannabinol (THC), can have a protracted effects later in life as a consequence of prenatal or adolescent exposure relevant to psychiatric diseases and can contribute to behavioral abnormalities in subsequent generations.

In current studies by Hurd and colleagues, F1 offspring with parental THC exposure (administered during adolescence and mated as adults) were observed to have impaired reward motivation and a spectrum of anxiety/compulsive behaviors. Intriguingly, F1 offspring without direct exposure to THC themselves had increased body weight suggesting that parental germline exposure could potentially induce epigenetic inherited metabolic dysregulation, possibly mediated through alterations in endocannabinoid function.

These findings suggest that cannabis during one's own lifetime can influence feeding behavior and potentially physiological parameters relevant to metabolism and energy balance in subsequent generation to impact body weight.

Research was supported with funds from the National Institute of Drug Abuse and the National Institutes of Health.

Speaker Summary (685.06)

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Insulin and Sweetened High Fat Food Modulates Reward Circuitry

Minisymposium: *Food for Thought: Experiential, Hormonal, and Neural Antecedents of Obesity*
Wednesday, Nov. 13, 8:30–11 a.m., Room 6E

Insulin — prompted by a sweetened, high fat meal — has been found to play a central role in decreasing the rewarding properties of food-related cues. Insulin caused a decrease in strength of neuronal communication onto dopamine-releasing neurons that relay information about the value of food rewards. The discovery of how insulin works at the molecular level in the reward system leads to a greater understanding of how one becomes less interested in food-related cues after having a high calorie meal.

This study, published in the February issue of *Nature Neuroscience*, focused on insulin's role in suppressing communication to neurons that release dopamine in a brain region known as the ventral tegmental area (VTA). When insulin was applied to the VTA, mice no longer gravitated towards environments where food had been offered, nor did they exhibit heightened anticipatory activity when faced with food-related cues.

Insulin application to dopamine neurons from mouse brain slices caused a long lasting inhibition of glutamate release onto dopamine neurons by a mechanism involving endogenous cannabinoids. This fundamental change in the neurons, called long-term depression, is known to be critical for selectively weakening specific synapses and reducing the output of information from the affected neurons. This weakening of synaptic strength was mimicked when mice had elevated endogenous insulin levels due to eating sweetened high fat food for one hour.

This effect expected to reduce the output of dopamine-releasing neurons. Indeed, in unpublished work to be presented at the Society for Neuroscience meeting, insulin applied to VTA reduces dopamine release. Taken together, this study describes the cellular mechanism underlying why cues in our environment that predict food (McDonalds golden arches, for example) are less salient to us when we are sated, as opposed to when we are hungry. Future work will be directed at determining the effects of insulin on reward circuitry during pathological situations, such as hyperinsulinemia or in models of obesity.

This research was supported by the Canadian Institutes of Health Research.