activations in the striatum and insula correlated with food craving in obese but not lean individuals. Together, these findings suggest important differences in obese and lean individuals with respect to activation patterns in motivational neurocircuitry that may promote eating behaviors.

Importantly, metabolic measures were also collected. Brain activations during all three conditions correlated with a homeostatic measure of insulin resistance (HOMA-IR) in obese but not lean individuals in regions including the insula, inferior frontal gyrus, striatum, and thalamus. Furthermore, regional brain activations (eg, in the thalamus during the favorite-food cue condition and striatum and insula during the stress condition—Figure 1) were found to mediate the relationship between HOMA-IR and food craving in obese (but not lean) individuals. These findings suggest that interventions that target motivations rather than energy balance *per se* may be particularly relevant to combating obesity in the current environment.

The current study helps integrate findings from multiple disciplines. Such integrative research may help address current debates about how best to conceptualize and treat obesity and ultimately lead to improved treatment strategies. Additionally, identifying clinically relevant subgroups with obesity (eg, those with binge-eating disorder, a condition hypothesized to show particular similarities with addictions (Gearhardt *et al*, 2011b), including in brain activations relating to reward processing (Balodis *et al*, 2013)), may help resolve current debates and target interventions.

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Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD *et al* (2013). Monetary reward processing in obese individuals with and without binge eating disorder. *Biol Psychiatry* **73**: 877–886.

Danaei G, Ding EL, Mozzaffarian D, Taylor B, Rehm J, Murray CJL *et al* (2009). The preventable causes of death in the United States: Comparative risk assessment of dietary, lifestyle and metabolic risk factors. *PLoS Med* **6**: e1000058.

Gearhardt AN, Grilo CM, DiLeone RJ, Brownell KD, Potenza MN (2011a). Can food be addictive? Public health and policy implications. *Addiction* **106**: 1208–1212.

Gearhardt AN, White MA, Potenza MN (2011b). Binge eating disorder and food addiction. *Curr Drug Alcohol Rev* **4**: 201–207.

Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN (2013). Neural correlates of stress- and food-cue-induced food craving in obesity: Association with insulin levels. *Diabetes Care* **36**: 394–402.

Ziauddeen H, Farooqi IS, Fletcher PC (2012). Obesity and the brain: how convincing is the addiction model? *Nat Rev Neurosci* **13**: 279–286.

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Targeting Emotion Circuits with Deep Brain Stimulation in Refractory Anorexia Nervosa

There is an urgent need to develop novel therapies for patients with anorexia nervosa (AN). A condition that is heterogeneous, highly resistant to treatment, and associated with striking rates of morbidity and mortality, few therapeutic advances specifically for AN have been made in the past 150 years. A re-orientation in the last two decades toward neuroscientific explanations for AN offers hope that an increased understanding of the illness' neural roots will lead to better treatments (Kaye *et al*, 2009).

Deep brain stimulation (DBS) is a neurosurgical procedure that targets critical nodes in dysfunctional neural circuits driving pathological behaviors (Lozano and Lipsman, 2013; Mayberg *et al*, 2005). DBS' efficacy in disorders like Parkinson's Disease has driven its investigation in other circuit-based conditions, including major depression (Lozano and Lipsman, 2013). Several factors led us to consider DBS in refractory AN. First, the primarily limbic structures implicated in the disorder, largely by functional neuroimaging, are consistent with the clinical observations that AN is predominantly a disorder of emotional processing. Further, the ability of DBS to safely and effectively access limbic nodes in mood- and anxiety-related circuits suggested that it could be applied to AN, a disorder marked by high rates of depressed mood and affective dysregulation.

The subcallosal cingulate (SCC) has a key role in modulating emotional states and projects cortically, to medial- and orbitofrontal cortex, as well as subcortically to nucleus accumbens. Our group has also shown that SCC neurons participate directly in emotion processing, responding preferentially to affective-laden stimuli and decisions (Lipsman *et al*, 2013a). The SCC is thus both structurally and

functionally integrated into emotion pathways, and its activity linked to disorders of emotion.

Our initial experience in a small group of treatment-refractory patients ($N=6$; average age: 38 years; average illness duration: 18 years) showed DBS to be reasonably safe in AN, and associated with improvements in comorbid mood and anxiety symptoms (Lipsman *et al*, 2013b). These results were maintained during 6 months of clinical follow-up, with significant reductions in depressed mood and anxiety translating, over time, into increases in BMI (Figure 1). Although time spent on eating- and weight-related preoccupations and rituals did decrease (Lipsman *et al*, 2013b), we believe the primary effect of DBS was an improved utilization of conventional AN treatment as a result of improved mood and affective regulation.

The influence of focal stimulation on global cerebral metabolism can be investigated with functional imaging, such as positron emission tomography (PET; Figure 2). PET studies in both AN and depression patients have shown significant network-wide changes in glucose utilization with DBS of the SCC. For example, after 6 months of DBS, both patient groups see significant activity reductions in the SCC and insula, as well as significant activity increases in the parietal lobe (Lipsman *et al*, 2013b; Mayberg *et al*, 2005). In AN, this change in parietal activity constitutes an effective reversal of known baseline parietal hypometabolism seen in acutely ill AN patients (Delvenne *et al*, 1996). These results confirm that although DBS is a focal, targeted therapy, it can influence metabolism in remote regions, and that AN-relevant structures, such as those governing mood, emotion regulation, and body perception, can be modulated by SCC stimulation.

Determining the potential role of DBS in the AN treatment algorithm will await the results of larger, sham-stimulation trials. It is clear, however, that the condition's physical and emotional symptoms are inextricably linked, and novel treatment strategies will need to address both in equal measure, to offer patients hope for a meaningful and enduring recovery.

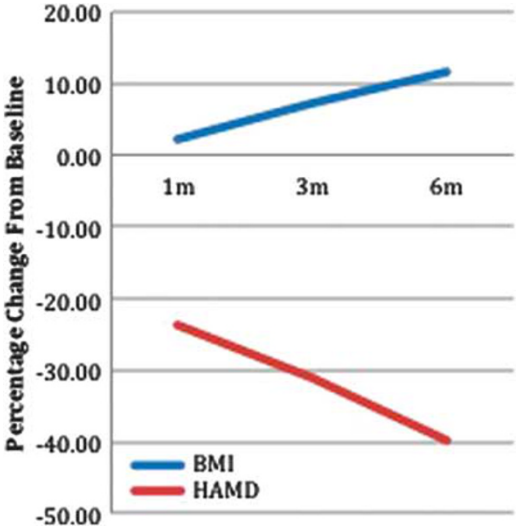

Figure 1. Mean ($N=6$) percentage changes from baseline, of weight and depression ratings, at each study time point (1 month, 3 months, and 6 months). At 6 months post-DBS, the cohort experienced a mean 12% increase in BMI and a 40% reduction in depression ratings. BMI, body mass index; HAMD, Hamilton Depression Rating Scale.

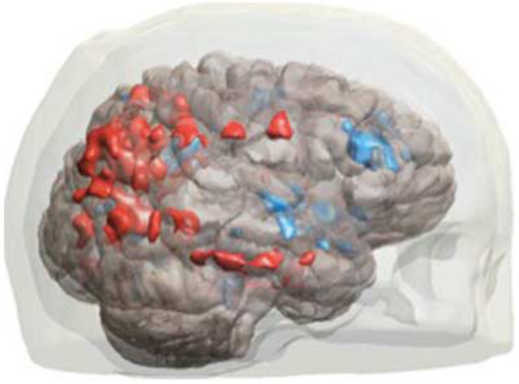

Figure 2. Three-dimensional rendering of composite cerebral metabolic changes in six patients who underwent deep brain stimulation of subcallosal cingulum for anorexia nervosa. Red indicates areas of increased activity following 6 months of stimulation compared with baseline, and blue indicates areas of decreased activity compared with baseline. Parietal regions, which are hypometabolic in AN patients, saw significant activity increases with chronic stimulation, and prefrontal areas, including the subcallosal cingulate, saw activity decreases.

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Delvenne V, Goldman S, De Maertelaer V, Simon Y, Luxen A, Lotstra F (1996). Brain hypometabolism of glucose in anorexia nervosa: normalization after weight gain. *Biol Psychiatry* **40**: 761–768.
Kaye WH, Fudge JL, Paulus M (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. *Nat Rev Neurosci* **10**: 573–584.
Lipsman N, Kaping D, Westendorff S, Sankar T, Lozano AM, Womelsdorf T (2013a). Beta coherence within human ventromedial prefrontal cortex precedes affective value choices. *NeuroImage* S1053-8119: 00607–1.
Lipsman N, Woodside DB, Giacobbe P, Hamani C, Carter JC, Norwood SJ *et al* (2013b). Subcallosal cingulate deep brain stimulation for

treatment-refractory anorexia nervosa: a phase 1 pilot trial. *Lancet* **381**: 1361–1370.
Lozano AM, Lipsman N (2013). Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron* **77**: 406–424.
Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C *et al* (2005). Deep brain stimulation for treatment-resistant depression. *Neuron* **45**: 651–660.

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Proteomic Biomarkers for Brain Disorders: Technical Considerations and Challenges

Proteomic technologies are being used to identify fluid-based biomarkers for detection, progression, and therapeutic response in brain disorders. This commentary focuses on the technical obstacles and challenges involved in the discovery, evaluation, and validation of such markers.

Following the initial excitement in the mid-90s that proteomics would yield definitive blood patterns to characterize tumor types, the proteome was explored in brain disorders, using cerebrospinal fluid (CSF) and plasma, with the expectation that these biofluids would reflect disease state and evidence of drug action. Conflicting results from a decade of studies and an international Human Proteome Project (http://www.thehpp.org/) highlight the need to revisit basic principles: standardization of protocols and sample collection, reproducibility of technology platforms (Mattsson *et al*, 2013) and controlling for false positives.

The Neuroscience Steering Committee of the Biomarkers Consortium (http://www.biomarkersconsortium.org/) undertook a proteomic analysis of plasma and CSF samples collected in the Alzheimer's Disease Neuroimaging (ADNI) study. A multiplex Luminex-based immunoassay panel was used to analyze plasma and CSF samples from AD, mild cognitively impaired and control subjects at baseline and 1 year. Several markers differentiated patients from controls; three proteins were consistent with earlier CSF studies, supporting the potential of plasma markers as a screening tool (Soares *et al*, 2012). Unfortunately, variability in inter-assay performance can lead to nonreplicable findings. CSF findings from the same ADNI subjects using a subset of the same multiplex panel, replicated only a few previously reported protein differences (Siuciak *et al*, 2012). Comparisons of plasma *vs* CSF profiles using the same platform make clear that only in a few instances are analytes sufficiently correlated to allow the use of plasma as a proxy for CSF (Potter *et al*, 2012). Thus, even with the ADNI studies, where standardized sample and proteomic protocols were used, variation in specific multiplex immunoassay analyte findings limits the interpretation of the results.

An emerging strategy views broad proteomic profiling of samples as 'exploratory' to be followed by highly sensitive, specific and reproducible assays targeted to one or more specific analytes. At the current stage of development, no multiplex immunoassay-based approaches that target >10 analytes have proved sufficiently sensitive to detect beta-amyloid and tau in CSF at the level achieved when optimizing conditions to simultaneously measure these analytes (Kang *et al*, 2012). Mass spectrometric-based assays offer an unbiased discovery approach (Craft *et al*, 2013); studies are underway with the same CSF ADNI samples allowing for a unique contrast to the multiplex immunoassay approach. Informatics and pathway analysis approaches can also be used to analyze proteomic data, but there is a tension between application of such methodologies and reproducibility of measures within a proteomic platform. High costs ($>$\$500 per sample) and limited aliquots (especially for CSF) are factors to consider in further attempts to replicate or rule out findings, which if true, could prove important.

To realize the potential of proteomics, it is critical to understand the limitations of the technology platforms (eg, its analytical performance—sensitivity, specificity, precision, stability, and reproducibility) and set standards for replication and verification of assay findings to advance promising markers to clinical application. In December of 2013, the Biomarkers Consortium will sponsor a workshop (https://www.signup4.net/public/ap.aspx?EID=CSFP11E&TID=WhpjeshOarRyJDUAXwZjKg%3d%3d) focused on characterizing the CSF proteome and developing guidelines for use of technologies platforms to better identify reliable markers of brain disease.

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Craft GE, Chen A, Nairn AC (2013). Recent advances in quantitative neuroproteomics. *Methods* **61**: 186–218.
Kang JH, Vanderstichele H, Trojanowski JQ, Shaw LM (2012; Simultaneous analysis of cerebrospinal fluid biomarkers using microsphere-based xMAP multiplex technology for early detection of Alzheimer's disease. *Methods* **56**: 484–493.
Mattsson N, Andreasson U, Persson S, Carrillo MC, Collins S, Chalbot S *et al* (2013). CSF biomarker variability in the Alzheimer's Association quality control program. *Alzheimers Dement* **9**: 251–261.
Potter WZ, Pickering EH, Immerman F, Kuhn M, Siuciak J, Shaw L. Alzheimer's Disease Neuroimaging Initiative (ADNI), the Foundation for NIH Biomarkers Consortium CSF Proteomics Project Team (2012). *Cerebrospinal fluid (CSF) vs plasma-based biomarkers in Alzheimer's disease (AD), mild cognitive impaired (MCI) and age-matched healthy controls (HC) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Alzheimers Dement* **8**: P217.
Siuciak JA, Pickering EH, Immermann F, Kuhn M, Shaw L, Potter WZ. Alzheimer's Disease Neuroimaging Initiative (ADNI), the Foundation for NIH Biomarkers Consortium CSF Proteomics Project Team (2012). *Cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease (AD), mild cognitively impaired (MCI) and age-matched healthy controls (HC) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Alzheimers Dement* **8**: P216–P217.
Soares HD, Potter WZ, Pickering E, Kuhn M, Immermann FW, Shera DM *et al* (2012). Plasma biomarkers associated with the apolipoprotein E genotype and Alzheimer disease. *Arch Neurol* **69**: 1310–1317.

Neuropsychopharmacology Reviews (2014) **39,** 252; doi:10.1038/npp.2013.202