We recently completed a microarray analysis to identify changes in gene expression in response to a brief (5 days) and moderate (<10% weight loss) reduction in food intake (Guarnieri *et al*, 2012). Analysis was conducted on RNA from four brain regions: ventral tegmental area, prefrontal cortex, hypothalamus and nucleus accumbens. Stress responsive genes were prominent in the list of genes that change after restriction, and corticosterone was shown to be necessary and sufficient for many of these changes. There were some surprises in these results that deserve emphasis: (1) the gene changes occurred rapidly (within the first 24 h of restriction) before any weight loss was apparent and (2) the expression changes detected were not restricted to one region, and usually were seen in 2–4 of the regions surveyed. This fast and universal response was not something that was anticipated, but is reasonable if a systemic factor such as corticosterone is the key signal. Finally, the changes seen were implicated in increased food motivation that occurred after restriction.

Previously published work supports the role of stress response in mediating effects of caloric restriction. Work from the Bale lab has shown that a longer (21 days) caloric restriction leads to stress pathway activation, including corticosterone as well as corticotropin-releasing factor (CRF) in the bed nucleus of the stria terminalis (Pankevich *et al*, 2010). Restriction increased stress responses as well as binge eating. Interestingly, the changes in CRF did not reverse upon re-feeding, and subsequent analysis showed that the CRF regulatory sequences also maintained altered methylation patterns. Moreover, withdrawal from high-fat food produced similar adaptions in gene expression and chromatin state.

Other work with animals exposed to high-fat diet also supports a role for chromatin changes and transcriptional adaptation within dopamine circuits. Reyes and colleagues (Vucetic *et al*, 2011) have shown specific gene changes in the nucleus accumbens following long-term high-fat-diet exposure. Specifically, decreases in mu-opioid receptor expression correlated with increased methylation and MECP2 binding in the proximal regulatory regions. Moreover, H3K9 methylation was increased and acetylation was reduced, which is consistent with an inactive chromatin state.

In sum, changes in metabolic state can have specific and significant effects on the transcription profile of the brain. These changes are mediated by alterations in chromatin and, most importantly, are likely to have a role in behavioral adaptation to different food environments.

Defining these molecular responses will help us to understand how intake and weight control is influenced by previous metabolic experience. These pathways are targets for potential therapeutics that can reverse or otherwise modulate this plasticity and help with weight loss. Moreover, as with drugs of abuse, stress is a common cause for loss of control over eating. The above work suggests that the brain might interpret stress hormones as a state of hunger, and should inspire stress response attenuation as a potential therapeutic strategy for obesity.

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DISCLOSURE

The authors declares that, except for income received from my primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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Neurobiological Correlates of the Familial Risk for Stimulant Drug Dependence

Stimulants such as cocaine and amphetamines are popular recreational drugs, which are thought to be used by up to 52 million individuals worldwide (UNODC, 2010). However, despite their high addictive liability, not everyone who uses these drugs develops dependence, though the risk for dependence is significantly increased for people with a family history of addiction. This familial aggregation of drug and alcohol dependence suggests that either genetic factors, a shared family environment, or an interaction of genes and environment underlie the increased risk for addiction in some people. The concept of endophentoypes may offer a useful tool to better understand how a pre-existing vulnerability to addiction might be inherited. *Endophenotypes* have been described as neurobiological correlates of a disorder, which are thought to be genetically determined and stable over time (Gottesman and Gould, 2003). In other words, abnormalities in brain systems underlying the clinical symptoms of stimulant dependence may not only be observed in individuals who are dependent on stimulant drugs, but also in their non-dependent first-degree relatives. Key symptoms of stimulant dependence, such as the inability to stop using the drug and the loss of control over drug intake, may be underpinned by a general lack of self-control, which may have predated drug-taking.

We assessed a wide range of cognitive and emotional functions as well as personality traits that have previously been associated with drug dependence in three groups of volunteers: 50

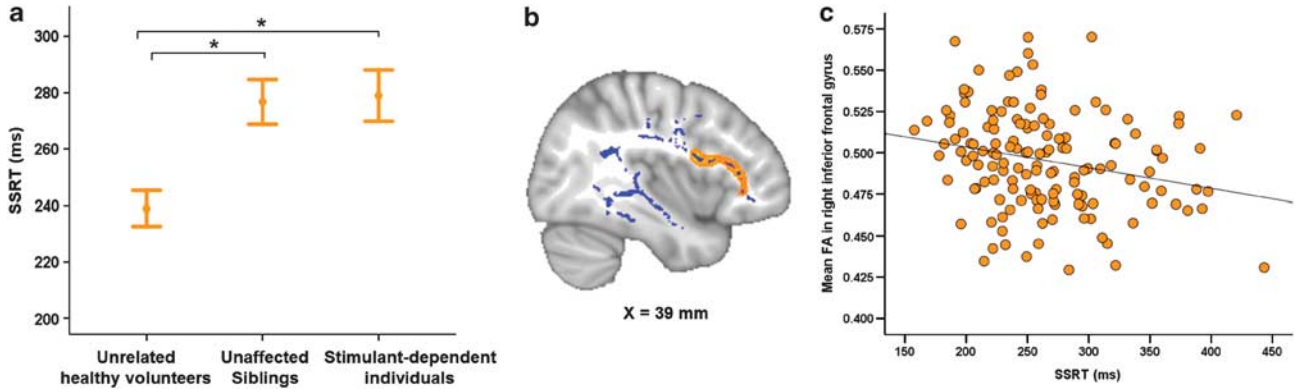

Figure 1. Deficits of motor inhibitory control and white matter organization in stimulant-dependent individuals and their non-dependent siblings. (a) Stop-signal reaction time (SSRT) differed significantly between the three groups ($F_{2,141} = 9.9$, $P < 0.001$). SSRT was significantly prolonged in both the stimulant-dependent individuals and their siblings compared with unrelated healthy volunteers (Bonferroni $P \leqslant 0.005$, for both comparisons). (b) The skeleton of group differences in mean fractional anisotropy (FA) is colored in blue ($F_{2,141} = 26.3$, $P < 0.001$); on the basis of prior literature, regions of interest were selected within the blue skeleton, which included the inferior frontal gyrus and the pre-supplementary motor area (colored in orange). (c) Scatterplot showing that participants with greater FA in the right inferior frontal gyrus had better inhibitory performance (shorter SSRT) on the stop-signal task ($r_{142} = 0.24$, $P < 0.005$). From Ersche *et al* (2012a). Reprinted with permission from American Association for the Advancement of Science.

adults with stimulant dependence, their non-dependent biological siblings and 50 unrelated healthy volunteers who had neither a personal nor a family history of dependence (Ersche *et al*, 2012a, 2012b). We identified significant impairments in inhibitory control abilities and abnormally high levels of impulsive and compulsive personality traits in the sibling pairs compared with the unrelated healthy volunteers. The sibling pairs also shared abnormalities in brain regions that have previously been associated with stimulant dependence, such as the inferior frontal gyrus, the amygdale, and the putamen (Chang *et al*, 2005; Lim *et al*, 2002). Moreover, their poor performance of behavioral control on the stop-signal task was directly associated with reduced fractional anisotropy in frontal white matter brain fibers, shown in Figure 1.

These findings shed new light on addiction vulnerability and may explain why the risk of becoming addicted to drugs is increased in people with a family history. The observation that abnormalities in brain and behavior may render individuals vulnerable to developing dependence (if resilience factors are absent), opens up new avenues for preventative and therapeutic strategies. For example, preventative approaches may consider strengthening self-control abilities in individuals at risk, while therapeutic interventions could be guided by the successful compensatory strategies used by unaffected siblings to overcome their brain abnormalities in every-day life. The identification of addiction endophenotypes in brain and behavior provide further compelling evidence that drug dependence is a disorder of the brain, with underlying abnormalities that can increase a person's risk for addiction.

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Epigenetic Regulation of Synapsin Genes in Mood Disorders

The synapsins are a family of neuronal phosphoproteins consisting of *SYN1* at chrXp11.3, *SYN2* at chr3p25, and *SYN3* at chr22q12.3 with alternative splicing leading to as many as 10 isoforms. They are involved in synaptic transmission and plasticity, as well as various stages of neurodevelop-