motivated behavior that is controlled not just by metabolic and homeostatic factors, but also by environmental factors such as emotion and the hedonic nature of the food itself. Yet, little is known about how brain regions involved in cognition and emotion might contribute to overeating, and therefore, obesity. In order to probe this neural circuitry, we recently developed and validated a simple and rapid task in which cues associated with food availability can later lead to increased food consumption in sated mice (Stern et al. Molecular Psychiatry 2018). We then utilized this task in order to describe the mechanisms by which the brain coordinates conditioned overconsumption.

Methods: We used immediate early gene mapping to examine brain regions that are activated during Ctx-IF. We then used pharmacological and chemogenetic methods to inactivate the insular cortex and specifically the IC → central amygdala (CeA) projection to determine whether this circuit was required for cue-mediated overconsumption. We then profiled the projection neurons from the insular cortex to the CeA using retro-TRAP (Retrograde - Translating Ribosome Affinity Purification). We injected the retrograde canine adenovirus, CAV-GFP, into the CeA of SYN-NBL10 mice which contain anti-GFP–tagged ribosomal subunit proteins. Two weeks later, we dissected out the insular cortex and immunoprecipitated GFP, therefore pulling down polysome-bound, translating mRNAs of neurons that project to CeA. High-throughput RNA sequencing allowed us to identify markers for this projection and tested their function in the overconsumption task.

Results: In the conditioned overconsumption task, sated mice reliably consume more in the context previously paired with food than in the unpaired context. We found that the insular cortex and central amygdala, among others, are activated in sated mice following the consumption test. Furthermore, we find that the insular cortex, and specifically, the insular cortex → CeA projection, is required for overconsumption, but not for homeostatic feeding measured over 24 hours. Using retro-TRAP, we then identified neuronal nitric oxide synthase 1 (nos1) and vesicular glutamate transporter 2 (slc17a6) as markers for this projection. Chemogenetic inhibition of insular cortex Nos1 neurons also prevented cue-mediated overconsumption, which occurs through suppression of homeostatic satiety signals within the CeA.

Conclusions: We have identified a molecularly defined circuit from the insular cortex → CeA that controls conditioned overconsumption by suppressing homeostatic satiety signals. Interestingly, the insular cortex is not involved in homeostatic feeding, that is food intake over a 24 hour period or food intake following an overnight fast. This indicates that there is top-down control of feeding that is independent of homeostatic regulation, which may be relevant to understanding the pathogenesis of obesity and binge-eating disorder.

Keywords: Obesity, Amygdala, Insular Cortex, Eating Disorders, Molecular Profiling

Disclosure: Nothing to disclose.

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A Neuroeconomic Approach to Quantify the Subjective Cost of Self-Control and its Modulatory Factors: Stress, Risk and Ambiguity

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Background: The failure to use self-control to guide goal-directed behavior is a central problem for both healthy individuals and those with clinical disorders marked by pathological choice behavior (e.g., substance use disorder, excessive gambling and obesity). Emerging theoretical work suggests that deviations from goal-directed behavior may emerge from a decision-making process that weighs the costs of exerting cognitively demanding control against its perceived benefits. These 'control costs' are thought to stem from the limited cognitive resources available to support the demands of self-control. Here, we aimed to (1) develop an econometric approach to quantify the subjective cost of exercising self-control each individual, (2) to measure how these costs are modulated by changes in affective state, and (3) identify whether these costs are sensitive to different forms of uncertainty (risk and ambiguity).

Methods: Healthy, hungry (male and female) dieters first provided subjective ratings for food items, allowing us to identify a highly tempting food for each individual. Both before food exposure and at regular intervals after exposure, participants reported their willingness-to-pay in dollars to remove the tempting food for the remainder of the experimental period, effectively "pricing" their subjective cost for exercising self-control (Study 1: $N = 32$). We then measured how these costs differed in an independent cohort of dieters who first underwent exposure to an acute stressor (cold-pressor task), which is widely thought to compromise the use of self-control (Study 2: $N = 31$). Finally, in Study 3 ($N = 38$), dieters made a series of binary choices between spending a predictable amount of time with a highly-tempting food reward (certain option) or a lottery option, for which they could be required to spend a greater amount of time with this food (5-60 minutes; higher control costs), or no time at all (0 minutes; no control cost). Critically, the probability of each option was either stated explicitly (risk) or with some degree of uncertainty (ambiguity). We measured how much dieters were willing-to-pay to avoid temptation as an index of self-control costs (Study 1-2) and the proportion of lottery choices participants were willing to accept as an index of participants' tolerance for risk and ambiguity when making decisions regarding self-control (Study 3).

Results: Across Studies 1 and 2, we found evidence that individuals were willing to pay to avoid exposure to temptation, confirming that we can measure subjective control costs in units of "dollars" humans. Specifically, control participants paid ~17% of their $10 endowment (DOLLARS/min) to restrict exposure to tempting foods, while stressed participants paid significantly more to avoid temptation (~34%; DOLLARS/min; independent t-test: $t(61) = 2.65$, $p < 0.01$), suggesting that stress-related deficits in behavioral control may stem from higher subjective costs of control after stress exposure. In Study 3, participants revealed a marked aversion to uncertainty, such that they were less likely to choose lottery choices when the cost of self-control was not predictable. Specifically, participants chose fewer ambiguous lottery choices than risky ones (paired t-test: $t(37) = 3.44$, $p < 0.01$), suggesting they were averse to choice environments in which they could not fully predict the cognitive costs of self-control.

Conclusions: Consistent with an emerging framework viewing goal-directed control as a cost-benefit decision-making process, these data suggest that the subjective cost of self-control can be quantified in humans and that these costs are highly sensitive to changes in affective states. Our findings also suggest that tolerance for risk and ambiguity play a role in when choosers are willing to engage in self-control processes, pointing to new avenues of research that use these decision preferences to predict when individuals will use self-control.

Keywords: Self-Control, Decision-Making, Stress, Computational Psychiatry, Uncertainty

Disclosure: Nothing to disclose.