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Training Motor Responses to Food:

A Novel Treatment for Obesity Targeting Implicit Processes

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Abstract

The present review first summarizes results from brain imaging studies showing that people who exhibit greater brain reward and attention region response, and less inhibitory region response, to high-calorie food images and cues show elevated future weight gain. These data suggest that an intervention that reduces reward and attention region response to such food cues and increases inhibitory control region response may reduce overeating. This review then summarizes findings from cognitive psychology experiments showing that food response inhibition training and food response facilitation training decrease attentional bias for and intake of the training food, increase inhibitory control, and produce weight loss in overweight participants. These data suggest that food response training may represent a method for treating obesity. Based on this review, a new conceptual model is presented to describe how different response training procedures may contribute to modifying eating behavior. This review then summarizes results from a preliminary trial that found that a multifaceted food response training intervention reduced reward and attention region response to high-calorie food images, monetary valuation of high-calorie foods, and body fat loss compared to a generic response inhibition training control condition, which provide novel support for the thesis that response training may operate by reducing valuation of high-calorie foods. It is concluded that future research should evaluate the efficacy and mechanism of action for more intensive food response training interventions and test whether adding such interventions to extant weight loss treatments increases their efficacy.

KEYWORDS: neural vulnerability factors, prospective brain imaging, weight gain, obesity, inhibition, reward, attention, food, weight-loss treatment, response training, attentional retraining

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The prevalence of obesity has risen dramatically worldwide and is credited with 2.8 million premature deaths annually (World Health Organization, 2013). Yet the most common treatment, behavioral weight-loss interventions, almost never results in lasting weight loss (Butryn, Webb, & Wadden, 2011; Turk et al., 2009). Although bariatric surgery can produce more persistent weight loss, it is invasive, associated with medical complications, often contraindicated, and can cost over $30,000 (Colquitt et al., 2014; Martin et al., 2010; Puzziferri et al., 2014). Thus, it is vital to identify novel efficacious treatments for obesity.

Eating high-calorie foods increases activation in regions implicated in reward processing, including the striatum (caudate nucleus, putamen, nucleus accumbens), midbrain (ventral tegmental area, substantia nigra), amygdala, and orbitofrontal cortex (OFC; Kringelbach et al., 2003; Small et al., 2001). Accordingly, scientists have investigated whether individuals with elevated reward region responsivity to food are at increased risk for future excessive weight gain. Further, individuals with inhibitory control deficits are more sensitive to reward-predictive cues and are thus more vulnerable to the pervasive temptation of appetizing foods in our environment, which contributes to overeating (Diergaarde et al., 2009; Sutin, Ferrucci, Zonderman, & Terracciano, 2011). In addition, inhibitory control regions modulate responsivity of reward regions (Hare, Camerer, & Rangel, 2009). Therefore, scientists have also tested whether individuals with weaker responsivity of inhibitory regions are at risk for future weight gain. Prospective brain-imaging studies indicate that elevated responsivity of reward regions and lower responsivity of inhibitory control regions to food cues (e.g., images of high-calorie foods) predict future excessive weight gain (e.g., Yokum, Ng, & Stice, 2011). These findings appear to be generally consistent with the dual-systems theory, which posits that overeating results from a strong automatic approach response to high-calorie food and food cues that is coupled with a weak inhibitory region response (Hofmann, Friese, & Strack, 2009; Wiers et al., 2007).

The evidence that individuals who show elevated reward region response to food cues and weaker inhibitory region response to such cues are at elevated risk for future weight gain suggests that interventions that reduce reward region responsivity and increase inhibitory region responsivity to food cues might prove useful in the treatment of obesity. Fortunately, cognitive science experiments indicate that training people to inhibit a behavioral response to high-calorie food, which may target these neural vulnerability factors, produces weight loss (e.g., Veling, Koningsbruggen, Aarts, & Stroebe, 2014), suggesting that food response-inhibition training may represent an efficacious strategy for treating obesity. Such translational neuroscience and cognitive science research holds great promise because it is based on objective behavioral and biological data from rigorous experiments. Further, response-inhibition training targets bottom-up implicit, automatic processes in response to food cues, rather than relying on top-down conscious control and sustained caloric deprivation like most current behavioral treatments.

The aim of the present review is to summarize results from prospective brain imaging studies focused on identifying neural vulnerability factors that predict excessive weight gain, and to review findings from cognitive psychology experiments that have evaluated various interventions that involve food response inhibition or food response facilitation training that may reduce these neural vulnerability factors and have produced weight loss effects. To discuss possible common mechanisms across these different interventions, the review focuses on intervention tasks in which manual responses to images of food are manipulated. Accordingly, interventions to change responses toward food that do not include manual responses as a central component, e.g., different kinds of conditioning procedures (e.g., Hollands, Prestwich, & Marteau, 2011; Baeyens, Eelen, Van den Bergh, & Crombez, 1992) are not discussed. The review focuses specifically on interventions that are assumed to target automatic approach responses and poor inhibitory control toward food, as well as biased attentional processing. As detailed below, we included interventions focusing on attentional processes that include a response component because they appear to represent an alternative vehicle for training motoric responses. Further, because people devote more attention to stimuli they find rewarding (Pessoa, 2016), re-directing attention away from high-calorie foods may also prove useful in the treatment of obesity. Important parallels with alcohol consumption research are drawn where relevant for exploring the proposed mechanisms of the training tasks. Based on this review a new conceptual model is presented to describe how different cognitive training procedures may modify eating behavior. This model can be used to predict whether there is added value in combining different training tasks. We then summarize findings from a preliminary trial that evaluated the effects of a multi-faceted food response training intervention in the treatment of obesity and investigated the mechanism of effects for this intervention using brain imaging. Important directions for future research to extend this program of study are then highlighted.

1. Neural Vulnerability Factors that Predict Future Weight Gain

Obese versus lean humans show greater response of brain regions implicated in reward/motivation (striatum, amygdala, OFC) and attention (anterior cingulate cortex [ACC]) to high-calorie food images (e.g., Frankort et al., 2012; Holsen et al., 2012; Martin et al., 2010; Stice et al., 2010; Stoeckel et al., 2008). Obese versus lean humans also show greater recruitment of motor response regions when exposed to high-calorie food images (Brooks et al., 2013;

Jastreboff et al., 2013; Pursey et al., 2014), consistent with the known elevated motor excitability and automatic approach responses elicited by palatable foods and their cues for obese versus lean humans (Chiu et al., 2014; Meule et al., 2014; Freeman et al., 2014, 2015); these findings suggest an elevated motor approach tendency in obesity. The evidence that obese individuals show greater responsivity of reward, attention, and motor regions to food cues relative to their lean counterparts has been confirmed in a large meta-analytic review of cross-sectional studies (Pursey et al., 2014), indicating that these relations are robust. Behavioral data likewise demonstrate that obese versus lean humans show greater attentional bias for high-calorie food images according to Stroop tests (Braet & Crombez, 2003; Nijs et al., 2010a), dot-probe tasks (Kemps, Tiggemann, & Hollitt, 2014a), and eye-tracking (Castellanos et al., 2009; Graham et al., 2011; Werthmann et al., 2011). Further, elevated reward region response to palatable food images and receipt of such foods predicted greater *ad lib* food intake (Lawrence et al., 2012; Nolan-Poupart et al., 2013), as did attentional bias for high-calorie food (Nijs, Muris, Euser, & Franken, 2010b; Werthmann, Field, Roefs, Nederkoorn, & Jansen, 2014).

Although it is reassuring that these cross-sectional studies have produced relatively consistent effects, they cannot determine whether elevated reward and attention region responsivity to high-calorie foods predates overeating and subsequent weight gain, or conversely whether this heightened responsivity is a result of overeating or obesity. High-risk and prospective designs are necessary to establish temporal precedence. One high-risk study found that healthy weight adolescents at high versus low risk for future weight gain based on parental obesity show greater responsivity in regions implicated in reward processing (caudate, putamen, OFC) of high-calorie food tastes and monetary reward (Stice et al., 2011). More critically, prospective functional Magnetic Resonance Imaging (fMRI) studies have found that elevated

OFC response to cues that signal impending presentation of high-calorie food images (Yokum et al., 2011), elevated nucleus accumbens response to high-calorie food images (Demos et al., 2012), elevated substantia nigra, ventral tegmental area, hypothalamus, anterior thalamus, ventral pallidum, and nucleus accumbens response to high-calorie food receipt (Geha et al. 2013), and elevated caudate response to high-calorie food commercials (Yokum, et al, 2014) predicted future weight gain in samples containing lean, overweight, and obese individuals. Again, the striatum (caudate, putamen, nucleus accumbens) and OFC play a role in reward processing, as do the ventral tegmental area and substantia nigra (midbrain) and ventral pallidum (basal ganglia). Elevated resting state activation in other regions implicated in reward processing (e.g., ventral medial prefrontal cortex [vmPFC]) has also predicted future weight gain (Dong et al., 2015), though research has not established a consistent relations between elevated resting state activation and greater responsivity of those regions to functional events (e.g., exposure to food images).

However, because it is possible that a history of overeating may have contributed to this elevated responsivity of brain reward regions, it is important to test whether elevated reward region responsivity to food stimuli predicts initial excessive weight gain. One study found that elevated OFC response to an image of a chocolate milkshake signaling impending receipt of chocolate milkshake among healthy weight adolescents predicted future excessive weight gain (Stice, Yokum, & Burger, 2015). Obese individuals who evidenced greater reward and attention region response to high-calorie food images also showed poorer response to behavioral weight loss treatment (Murdaugh et al., 2012), consistent with the notion that hyper-responsivity of these regions may maintain overeating.

The above brain imaging results converge with behavioral evidence indicating that healthy weight individuals who work longer to earn high-calorie snack foods in an operant food reinforcement paradigm, which presumably signals a greater valuation of high-calorie foods, also show elevated future weight gain (Epstein, Yokum, Feda, & Stice, 2014). They also converge with evidence that attentional bias for high-calorie food predicted greater future weight gain (Calitri, Pothos, Tapper, Brunstrom, & Rogers, 2010) and poorer response to weight loss treatment (Werthmann et al., 2015).

The evidence that elevated reward and attention region responsivity predicts future weight gain also aligns with evidence from controlled trials that weight loss reduces reward (e.g., ventral striatum, parahippocampal gyrus, putamen, insula) and attention region (e.g., visual cortex) responsivity to high-calorie food images (Cornier, Melanson, Salzberg, Bechtell, & Tregellas, 2012; Deckersbach et al., 2014; Ochner et al., 2011; Rosenbaum, Pavlovich, Leibel, & Hirsch, 2008). Weight loss has also been associated with concurrent reductions in food preference ratings for high-calorie foods relative to changes observed in waitlist controls (Deckersbach et al., 2014).

Results are consistent with the reward surfeit theory (Stice et al., 2008), which posits that humans who show greater reward region response to high-calorie food intake are at risk for overeating, and with the incentive sensitization theory (Berridge, 2010), which posits that intake of high-calorie foods results in an elevated response of reward regions to cues that are repeatedly associated with hedonic reward from intake of such foods via conditioning, and that this elevated reward region response to food cues prompts overeating. Such mechanisms can also account for recent observations that overweight relative to lean individuals show increased Pavlovian conditioning to food-associated cues (Meyer et al., 2015) and continued responding to food cues despite reinforcer devaluation (Horstmann et al., 2015), and that greater food cue reward learning propensity predicts elevated future weight gain (Burger & Stice, 2014). In sum, a wealth of cross-sectional and prospective brain imaging studies suggest that overeating and obesity are associated with increased food or food cue reactivity in neural regions associated with attention and reward, and that successful weight loss may result in reduced response in reward and attention regions to these food stimuli.

Obese versus lean humans have also shown weaker activation of regions that have been implicated in inhibitory control (vmPFC) in response to high-calorie food ads (Gearhardt et al., 2014), and lower dlPFC response to high-calorie food images predicted greater ad lib food intake over the next 3 days (Cornier et al., 2010). These findings are noteworthy because they emerged in fMRI paradigms that did not require a behavioral response or inhibition of a behavioral response, which one would typically expect in paradigms in which inhibitory regions are recruited. However, these findings converge with evidence that obese versus lean teens showed less activation of prefrontal regions (dlPFC, ventral lateral prefrontal cortex [vlPFC]) when trying to inhibit responses to high-calorie food images (Batterink et al., 2010). Obese versus lean humans also show behavioral response inhibition deficits on stop-signal and go/no-go tasks involving both food and non-food stimuli, and show a preference for immediate intake of high-calorie foods over larger serving of the foods that are delayed, which reflects an immediate reward bias (Batterink et al., 2010; Bonato & Boland, 1983; Nederkoorn, Coelho, Guerrieri, Houben, & Jansen, 2012; Nederkoorn et al., 2006; Sobhany & Rogers, 1985), which also suggests that they show an elevated approach tendency to high-calorie foods. A preference for immediate food reward over larger delayed food reward also predicted future weight gain in multiple trials (Evans, et al., 2012; Fransis & Susman, 2009; Schlam, et al., 2013; Seeyave et al., 2009). Similar results have emerged from studies that examined the relation of self-reported inhibitory control deficits to future weight gain (e.g., Anzman & Birch, 2009; Duckworth, et al., 2010). Young adults with less grey matter volume in key inhibitory control regions (superior frontal gyrus, middle frontal gyrus) also showed marginally greater future weight gain (Yokum, et al., 2011).

The findings reviewed above converge with evidence that children and adults with inhibitory control deficits show poorer response to weight loss treatment (Kulendran et al., 2014; Nederkoorn, Jansen, Mulkens, & Jansen, 2007; Weygandt et al., 2013) and less maintenance of weight loss over 1-year follow-up (Weygandt et al., 2015). Indeed, individuals that showed less recruitment of inhibitory control regions (dorsolateral prefrontal cortex) during a delay-discounting task showed significantly less weight loss in response to weight loss treatment (Weygandt et al., 2013) and less weight loss maintenance over 1-year follow-up (Weygandt et al., 2015). Results are consistent with the thesis that impulsive individuals are more sensitive to food cues and more vulnerable to the pervasive temptation of appetizing foods in our environment, which increases overeating (Pickering et al., 1995).

In sum, obese versus lean adults and adolescents at risk for future obesity due to family history show greater reward and attention region response to high-calorie foods, both of which predict future weight gain, suggesting that these represent neural vulnerability factors for overeating. There is also evidence that inhibitory control deficits constitute a risk factor for future weight gain and attenuate response to weight loss treatment. This suggests that interventions that reduce the automatic reward and attention region response to high-calorie foods and increase inhibitory control region response to such stimuli should decrease overeating rooted in exposure to omnipresent food cues and effectively treat obesity. We will first review findings of training procedures aimed at targeting inhibition, reward and attention responses to food stimuli, and then discuss possible unique and overlapping mechanisms of these training procedures.

2. High Calorie Food Response-Inhibition Training

Auspiciously, emerging cognitive psychology findings suggest that response inhibition training with high-calorie foods reduces reward and attention region response to such foods, reduces behavioral choice for such foods, and produces weight loss among overweight individuals (Lawrence et al., 2015b; Stice et al., 2016; Veling et al., 2014). These computerized training interventions aim to directly reduce the reward value of high-calorie foods and cues, and the relatively automatic approach tendencies toward high-calorie food that drive overeating, and should thus help to effect sustained behavior change (Marteau et al., 2012; Stice et al., 2016).

Basic science experiments, with largely female undergraduate student samples of normal-weight (average BMI between 18 and 25), show that repeatedly presenting high-calorie food images with signals indicating that participants should withhold a behavioral response in stop-signal or go/no-go tasks decreases later consumption of that food in laboratory experiments compared to when participants perform a control task in which they respond to the foods or to when they perform a control task in which they inhibit their responses to non-food (Houben, 2011; Houben & Jansen, 2011; Lawrence et al., 2015a; Veling, et al., 2011) A meta-analysis that focused specifically on the effects of these food inhibition tasks to reduce intake found a medium effect size across studies (*d* = .46; Turton, Bruidegom, Cardi, Hirsch, & Treasure, 2016). In addition, one study found a reduction in self-reported daily caloric intake among an overweight community sample (Lawrence et al., 2015b), and another found a reduction in ad libitum food intake among children (aged 7-10 years; Folkvord, Veling, & Hoeken, 2016). Furthermore, three of the studies mentioned above found that the effects on consumption were largely driven by participants scoring relatively high on dietary restraint (Houben & Jansen, 2011; Lawrence et al., 2015a; Veling, et al., 2011). As this paradigm directly trains participants to inhibit a motor response to pictures of the high-calorie training foods, we conceptualize this as *response-inhibition training*. Go/no-go response-inhibition training also reduced choice for, and selected serving size of, the high-calorie training food and increased choice for low-calorie non-training foods among students of mostly normal weight (Koningsbruggen et al., 2014; Veling et al., 2013a,b).

Critically, adult dieters recruited at a university (87% were students, of mostly normal weight) who completed go/no-go response-inhibition training in 4 6-min weekly sessions in which no-go signals were consistently (100% of the time) paired with 100 images of high-calorie foods and beverages and go-signals were consistently paired with 100 non-food images showed significant directly-measured pre-post weight loss whereas dieters randomized to complete a go/no-go task in which non-food images were paired with go and no-go cues on a 50:50 basis did not (Veling et al., 2014). As one would hope, only overweight participants showed weight loss effects (i.e., participants scoring 1 standard deviation above the mean BMI of that sample), suggesting that the training may be an effective weight-loss treatment for overweight individuals (Figure 1A). Overweight/obese adults recruited from the community for a weight loss trial who completed 4 10 min go/no-go training sessions in which high-calorie food images were always paired with no-go-signals and low-calorie food images were not, showed greater directly-measured weight loss versus controls who completed parallel response inhibition training with non-food images (Figure 1B; Lawrence et al., 2015b); the weight loss effects (2.2 kg) persisted through 6-month follow-up ($p = .01$; $d = .48$). Undergraduates of mostly normal-weight who completed 10-minute Internet-delivered stop-signal tasks daily for 10 days in which high-calorie food trials were paired with a stop-signal 50% of the time and low-calorie foods were never paired with stop-signals showed significantly greater weight loss than participants who completed a generic inhibition task in which stop-signals were paired with high-calorie and low-calorie foods 25% of the time and participants who were exposed to the same food images without any stop-signals (Allom & Mullan, 2015; Study 1); however, weight data were self-reported. The authors were not able to replicate this weight loss effect in a second trial in which weight was measured directly. The null finding may have occurred for two reasons. First, unlike the other two trials in which high-calorie foods were paired with an inhibition signal 100% of the time, high-calorie foods were only paired with inhibition signals 50% of the time in the Allom trials, which may have weakened the effects (Jones et al., 2016). Second, unlike the other two trials that involved overweight/obese individuals, 83% of the participants in the Allom studies were in the healthy weight range.

Parallel findings have emerged in the alcohol domain. Response-inhibition training for beer in heavy drinkers slowed response time to beer cues and reduced inhibitory response errors to beer cues (Jones & Field, 2013). Further, inhibition training decreased implicitly assessed positive attitudes toward beer, and reduced craving for beer, as well as immediate beer intake, and alcohol intake over 1-week follow-up (Bowley et al., 2013; Houben et al., 2011; Houben et al., 2012; Jones & Field, 2013). Together with the findings discussed earlier, the data suggest that response inhibition training can reduce approach towards and intake of both food and alcohol.

Two meta-analyses of 18-19 studies of response inhibition training to food and alcohol reported an overall small-moderate *d* effect size of .38, which increased to a moderate effect size of .47-.50 for stimulus-specific no-go training, which employs consistent stimulus-no-go associations (Allom et al., 2015; Jones et al., 2016). It has been suggested that consistent associations (e.g. 100%) between appetitive stimuli and no-go signals may facilitate learning of direct associations between appetitive stimuli and inhibition of behavior whereas less consistent associations (e.g 50%) may actually facilitate learning to inhibit behavior to the no-go signals rather than to the appetitive stimuli they are paired with (Best, Lawrence, Logan, McLaren, Verbruggen, 2015; Jones et al., 2016). That is because in the case of inconsistent mappings between appetitive stimuli and no-go signals the appetitive stimuli are no longer valid cues for inhibition within the context of the task, and hence people may start to rely more strongly on the no-go signals to guide their responses instead (Best et al., 2015; Livesey & McLaren, 2007). Research is needed to examine this seemingly important task characteristic more systematically.

3. Low-Calorie Food Response-Facilitation Training

The studies reviewed above show that response-inhibition training reduces approach behavior toward high-calorie foods. Recent work has examined whether training motor responses toward certain foods but not other foods results in increased approach behavior toward the training foods. Specifically, cue-approach training, in which people (weight status not-reported) were trained to make a rapid behavioral response to certain high-calorie food images consistently paired with an auditory response signal (25% of the trials) and to not respond to other high-calorie food images not paired with the response signal (75 % of the trials), resulted in more frequent choice and consumption of the high-calorie foods paired with the response signal versus those not paired with the response signal, with effects persisting over 2-month follow-up

(Schonberg et al., 2014a). Cue-approach training also resulted in greater attention to the foods paired with response signals (measured by eye-tracking) and increased fMRI-assessed activation of brain regions implicated in representing reward value (Schonberg et al., 2014a). Because this paradigm directly trains participants to make behavioral responses to high-calorie training foods, while indirectly training them to withhold responses to high-calorie non-training foods, we conceptualize this as *response-facilitation training*. Importantly, removing the behavioral responses and inhibition of responses from this training paradigm abolished the effects on food choice (Schonberg et al., 2014a), suggesting that the motor response element of this response-signal task is essential for its efficacy. Two important questions are: (1) whether this response-facilitation training could be used to increase approach towards healthy low-calorie foods, (2) and whether such an approach could help to substitute high-calorie foods with low calorie foods during weight loss attempts. With regard to the first question, one study found that cue-approach training can be used to increase choices for specific low-calorie foods (e.g., vegetables) among a student sample (of mostly normal weight; Veling et al., 2016). More work is needed to test whether this task can be used to substitute high calorie foods with low calorie foods among different populations to facilitate weight loss.

4. Training Responses Away from High-Calorie Food and Toward Low-Calorie Food

Two other prominent cognitive training tasks have focused on training motor responses toward or away from specific foods. These tasks are the attention bias modification (dot-probe) task and the approach-avoidance task. These tasks are somewhat different from the response-inhibition and response facilitation tasks, because the *direction* of a motor response is trained rather than responding or inhibiting a response *per se*.

First, in a food-specific dot-probe paradigm, participants were shown images in which chocolate foods were shown on one side of the screen and non-chocolate foods on the other (order counter-balanced), which were the critical trials (Kemps et al., 2014b). Participants (female undergraduates of mostly normal weight) were asked to respond as quickly as possible to indicate whether a visual probe appeared behind the left or right image during the critical trials. In the chocolate respond-away training condition the probe appeared behind the non-chocolate foods 90% of the time and behind the chocolate foods 10% of the time. This condition directly trains people to make a response to a probe presented away from chocolate foods. Conversely, in the chocolate respond-toward training condition the probe appeared behind the non-chocolate foods 10% of the time and behind the chocolate foods 90% of the time. This condition directly trains people to make a response towards a probe presented behind chocolate foods. Participants in the chocolate respond-away training condition showed greater reductions in attentional bias for chocolate foods, chocolate craving, and chocolate food intake versus participants in the chocolate respond-toward training condition (Kemps et al., 2014b; Kemps, et al., 2015). Reductions in chocolate intake persisted at 1-week follow-up for participants (female undergraduates of mostly normal weight) who completed five weekly response-training sessions, but not for participants who only completed a single training session (Kemps et al., 2015). Kemps et al. (2014a) found that a community sample of obese participants who completed respond-away from high-calorie food training showed a reduction in attentional bias for high-calorie food images used in the training paradigm versus those who completed response-toward high-calorie food training. Kakoschke et al. (2014) found that participants (female undergraduates of mostly normal weight) who completed response-toward low-calorie food training showed reduced attentional bias for the high-calorie food images used in the training paradigm and less consumption of high-calorie foods in a taste test versus those who completed response-toward high-calorie food training.

It is important to note that although the effects from the dot-probe training could be explained by the response-toward training to high-calorie foods in the control condition, this alternative interpretation does not apply to the food response inhibition trainings studied by Veling et al. (2014) and Lawrence et al. (2015b) that used non-food images in the control condition and did not include go-responses to high-calorie foods.

Of note, an attention modification paradigm lacking a behavioral response component (a cued saccade task; Werthmann et al., 2014) did not produce the significant shift in attentional bias among female undergraduates (of mostly normal weight) that has consistently emerged in the dot-probe training paradigm that included behavioral responses (Kemps et al., 2014a, 2014b). This pattern of findings echoes evidence that stop signal training with alcohol images reduced cravings for alcohol, whereas a saccade training task lacking a motor response element did not (Jones & Field, 2013). These findings appear to provide further evidence that the motor response element of this training is essential for its efficacy.

Dot-probe training, which also includes a motor-response element, has likewise reduced attentional bias for alcohol and alcohol intake. One uncontrolled trial with hazardous and harmful drinkers found that four weekly training sessions produced significant reductions in attentional bias for alcohol and alcohol intake through 3-month follow-up (Fadardi & Cox, 2009). Similarly, five training sessions resulted in an improved ability to disengage from alcohol cues and a delay in relapse time over 3-month follow-up compared to controls among alcohol patients in treatment (Schoenmakers et al., 2010).

The second paradigm that trains responses away from and toward food is approach-avoidance training, which has primarily shown efficacy in reducing approach biases for alcohol, although results in both the alcohol and food domain are mixed. In this paradigm participants repeatedly make an avoidance movement (e.g., pushing a joystick away) in response to pictures of high-calorie foods and an approach movement (e.g., pulling a joystick towards themselves) in response to pictures of another stimulus type (e.g., low-calorie foods). In the food domain, one post-test only experiment with female undergraduate students (weight status not reported) suggested that a single-session of approach training towards low-calorie food words and avoidance training away from high-calorie food words resulted in greater selection of low-calorie food versus high-calorie food options relative to controls who did the reverse training (Fishbach & Shah, 2006). Another study found that female undergraduate students (of mostly normal weight) trained to avoid chocolate subsequently ate less chocolate than when trained to approach chocolate (Schumacher, Kemps, & Tiggeman, 2016). However, three repeated-measures experiments with undergraduate students of mostly normal weight involving a single-session of approach training to low-calorie food pictures and avoidance training for high-calorie food pictures did not produce consistent effects on implicit or explicit food preferences or intake of high-calorie and low-calorie foods compared to a control training without systematic avoidance to high-calorie food (Becker, et al., 2014). It is possible that the nature of the control condition used across the studies explains the inconsistent findings; the two trials that used a control condition in which participants were trained to approach high-calorie foods found intervention effects (Fishbach & Shah, 2006; Schumacher et al., 2016), whereas the three trials that used a control condition in which participants were not trained to approach high-calorie foods consistently found null effects (Becker et al., 2014). However, it is also possible that the effects of this training paradigm have been inconsistent because it involves executing a motor response directly to both high-calorie and low-calorie foods, rather than training people to inhibit a behavioral response to high-calorie foods. It should be noted that the approach-avoidance training is also different from the dot-probe task, because in the latter people are trained to respond to an alternative option that is presented alongside the images of high-calorie food.

With regard to the alcohol domain, research has found that approach-avoidance training produced an avoidance bias, as operationalized by faster avoidance than approach responses, toward pictures of alcoholic beverages among heavy drinkers and alcohol dependent individuals, and was associated with lower relapse rates over 1-year follow-up after treatment in two separate trials (Eberl et al., 2013; Wiers, et al., 2010; Wiers, et al., 2011). However, another study was unable to replicate these effects in two trials with undergraduate drinkers (Lindgren et al., 2015).

5. Translational Neuroscience and Cognitive Science

The average effect for the three food response-inhibition training interventions that produced significant reductions in weight described above (Allom & Mullan, 2015, Lawrence et al., 2015b; participants with a relatively high weight of the Veling et al., 2014 sample) was Cohen's *d* = .61, a medium effect size, whereas a moderate effect size of .50 for stimulus-specific no-go response-inhibition trainings for various appetitive behaviors emerged from two meta-analytic reviews (Allom et al., 2015; Jones et al., 2016). Given that these interventions were only 40-100 minutes in duration and very easy to complete, this compares favorably to the average pre-post weight loss effect from much more intensive and effortful 6-month behavioral weight loss treatments (*d* = .85; Franz et al., 2007). We therefore think it would be useful to conduct additional research on the potential therapeutic effects of what we broadly term "response training" interventions for appetitive behaviors, particularly those involving more intensive and varied training activities (e.g., response-inhibition training for high-calorie foods, response-facilitation training for low-calorie foods, and dot-probe training to re-direct attention away from high-calorie foods and instead towards low-calorie foods).

A food response training weight loss intervention could have key advantages over standard weight loss interventions, including the fact that it targets implicit processes, rather than relying on conscious control to affect changes in eating. Whether what is learned in food response inhibition training is explicit or implicit is currently unclear, however preliminary findings suggest that both mechanisms may operate (Verbruggen et al. 2014b) and whether or not participants have explicit awareness of the underlying stimulus-response contingencies appears to have little effect on training-induced weight loss (Lawrence et al., 2015b). The treatment-of-choice for obesity (behavioral weight loss interventions) relies on top-down conscious control to reduce food intake. A drawback of such interventions is that they are resource dependent and thus fail when people are under stress or fatigued (Fishbach & Shah, 2006). The implication is that stress and fatigue should be less likely to precipitate overeating among participants who complete the implicit response training.

A second drawback with the fact that behavioral weight loss treatments require top-down conscious control is that individuals who seek obesity treatment often show deficits in inhibitory control, which is associated with poorer response to weight loss treatment and less weight loss maintenance (Nederkoorn et al., 2007; Weygandt et al., 2013; Weygandt et al., 2015).

A third drawback of behavioral weight loss interventions is that they typically involve acute caloric deprivation, which ironically increases the reward value of high-calorie foods (Fuhrer et al., 2008; Goldstone et al., 2009; Leidy et al., 2011; Stice et al., 2013). This may represent a key rate-limiting factor for the amount and persistence of weight loss from existing behavioral obesity treatment, explaining why most people regain the lost weight within a year or two.

In contrast, response training interventions, which reduce the elevated approach behavior toward high-calorie foods exhibited by obese individuals, relies on implicit training, which is most effective for precisely those that need it most – individuals with a pronounced approach tendency for high-calorie foods and low inhibitory control. Such computerized training aims to directly change the automatic cognitive motivational processes that drive overeating and should thus result in sustained behavior change (Marteau et al., 2012). Response training is also a very cost-effective intervention because it can be implemented via computer and even via the Internet. Thus, it would be inexpensive to use alone or in combination with extant weight loss treatments.

Theory and preliminary findings suggest that it is possible that weight loss effects from response training may persist, though the persistence of weight loss has not been tested beyond 6-month follow-up to date (Lawrence et al., 2015b). On a theoretical level, hyper-responsivity of reward and attention regions to food cues, which predicts future weight gain, emerges when people habitually consume high-calorie foods, resulting in an association between hedonic pleasure from those foods and cues that predict this hedonic pleasure (Berridge, 2010; Burger & Stice, 2011). That is, habitual intake of high-calorie foods is theoretically necessary for the emergence of increased reward and attention region response to high-calorie food cues. This theory is based on results from dozens of conditioning experiments with animals and humans (see Stice & Yokum, 2016 for a review of these studies). It is also consistent with evidence that adolescents who exhibit more potent cue-reward learning during a conditioning paradigm show elevated future weight gain (Burger & Stice, 2014). It follows that reduced habitual intake of high-calorie foods, which may occur after response training (Lawrence et al., 2015b), would attenuate this conditioning process and reduce reward and attention region response to food cues that drives overeating. Consistent with this theory, weight loss interventions that result in marked reductions in intake of particular high-calorie foods produce a concomitant reduction in cravings for those foods after 2 to 24 months (Alberts, et al., 2010; Batra et al., 2013; Martin et al., 2011; Rieber et al, 2013). Emerging data from randomized trials also suggest that the effects of response training may persist, although the effects over long-term follow up have not been evaluated. Lawrence et al. (2015b) found evidence that their response-inhibition training intervention produced weight loss effects that persisted through 6-month follow-up. Schonberg et al. (2014a) found that their brief response-facilitation training produced effects that persisted through 2-month follow-up. Alcohol avoidance-training significantly reduced relapse over 1-year follow-up among adults in treatment for alcoholism in two trials (Eberl et al., 2013; Wiers et al., 2011).

6. Mechanisms of Effect for Training

It is important to consider the mechanisms of effect of the various food response-training paradigms, as it may guide the development of optimally effective prevention and treatments using this therapeutic modality. Four mechanisms have been proposed to explain the effects of the various types of response training paradigms, which overlap with four recently proposed ways in which associative learning could influence action control (Verbruggen et al., 2014a). It should be noted that at present it is unclear whether each of these mechanistic theories applies to all types of response trainings discussed, or only to some (e.g., dot-probe training). It would therefore be premature to attempt to map the mechanistic theories to particular response training approaches.

6.1 Modification of motor responses

First, the training paradigms may result in *increased inhibition* of the motor (approach) response toward food. Response-inhibition training results in the automatic inhibition of a motor response, which may replace the approach response to high-calorie foods and their associated cues and increase inhibitory control to the food (Freeman et al., 2014; 2015; Verbruggen & Logan, 2008). Consistent with this account, motor slowing has been observed for no-go associated foods (Veling et al., 2011), and arbitrary or conditioned-appetitive (palatable beverage-associated) stimuli associated with no-go signals reduce motor excitability (Chiu et al., 2014; Freeman et al., 2014, 2015) and engage brain regions associated with inhibitory control (Lenartowicz et al., 2011). The extremely rapid (within 100 ms) suppression of motor excitability following an appetitive stimulus-no-go trial during training shows stimulus- and response-specificity (i.e. motor excitability is only suppressed for the same appetitive stimulus and response effector muscles on subsequent trials), leading to the suggestion that stimulus-no-go training recruits proactive inhibitory control mechanisms involving the pre-supplemental motor area, ventrolateral PFC, and striatum (Freeman et al., 2015). However, studies have yet to examine whether modified motor responses to food (and associated neural control mechanisms) mediate training effects on food intake and food choice.

It is also possible that training lowers inhibition toward low calorie food, based on the assumption that individuals who do not eat many low-calorie foods (e.g., vegetables) may recruit inhibitory regions when low-calorie foods are encountered. For instance, response-toward training or cued-approach training could potentially lower inhibition to low-calorie food by training responses toward these foods (Becker et al., 2014; Schonberg et al. 2014b). However, no published study has examined the effectiveness of cued-approach training in facilitating choices for low calorie foods (but see Veling et al., 2016 for an unpublished study), and a study focusing on creating approach responses toward low calorie foods by means of response toward training did not find any effects of this training procedure on response tendencies (Becker et al., 2014). Therefore, the possibility of whether training paradigms as reviewed here are effective in lowering inhibition to low-calorie food remains to be tested.

Response-away training may replace the automatic approach response to stimuli with an avoidance response (e.g., Wiers et al., 2010, 2011). Indeed, previous work has shown that response-away training can modify an initial approach bias toward alcoholic beverages into an avoidance bias compared to a non-alcohol control training condition (Wiers et al., 2011). However, this change in response tendencies did not mediate the effect of approach-avoidance training on treatment outcome (Wiers et al., 2011). With regard to food stimuli, one study found no consistent effects of approach-avoidance training on action tendencies (Becker et al., 2014). For these reasons, the possibility of training approach-avoidance responses to food is not included as a candidate mechanism in our conceptual model.

6.2 Changing food value

Second, there is emerging evidence that the training paradigms *modify the hedonic or motivational value of food.* Response inhibition training has been shown to reduce the hedonic and motivational value of a variety of no-go associated stimuli (e.g., positive images, erotic stimuli, neutral stimuli, alcoholic beverages; Bowley et al., 2013; Doallo et al., 2012; Ferrey, et al., 2012; Houben et al., 2012; Veling et al., 2008; Wessel et al., 2014). In adults, high-calorie foods are rated as less attractive and tasty following no-go training (Veling et al., 2013a) and this ‘stimulus devaluation’ may mediate the effects of training on reduced choice and intake of no-go food (Veling et al., 2013a; for similar effects on alcoholic beverages see Houben et al., 2012). Likewise, Lawrence et al. (2015b) found that participants showed a reduction in the evaluative ratings of foods paired with no-go signals; the degree of reductions in food liking correlated with the amount of training-induced weight loss (r = .30). Importantly, the devaluation of geometric shapes due to the pairing of some of the shapes with stop-signals has been specifically linked to motor inhibition, rather than to the aversiveness, effort, conflict, or salience associated with stop signals (Wessel et al., 2014). By extension, paradigms that do not pair foods with motor inhibition would *not* be expected to modify reward value and approach behavior because the motor suppression component appears to be crucial for this effect.

With regard to response-facilitation training it has been found that participants attached greater monetary value to high-calorie foods associated with respond signals versus those not associated with respond signals (although this value measurement was taken only after food choice; Schonberg et al., 2014a). Moreover, fMRI findings from the same study revealed that elevated activation in the vmPFC and ventral and mediodorsal striatal regions in response to high-calorie foods associated with response signals correlated with how often these foods were chosen by participants, consistent with the valuation theory, as these brain regions have been implicated in reward valuation (Schonberg et al., 2014a). Crucially, these brain regions also represent the motor effort (response vigor) associated with cues, using dopamine as a signaling agent to integrate predicted reward value and response effort into a “common neural currency” (Kroemer et al., 2014). This functional integration of reward value and motor effort (also termed ‘incentive salience’, Berridge et al., 2010) within nucleus accumbens and associated mesocorticolimbic regions suggest that consistently modifying a motor response to a cue can change its anticipated ‘reward’ value and reduce an approach bias. That is, it is possible that motor regions feed back to reward regions, such that repeatedly inhibiting behavioral approach responses to stimuli automatically reduces the valuation of those stimuli. If this is true, response inhibition training might represent an effective method of reducing appetitive desire to objects that cause health problems.

The stimulus devaluation effect of response-inhibition training and the increased value after response-facilitation training also fit with evidence for a hard-wired link between reward (or approach) and going, and punishment (or avoidance) and stopping (Guitart-Masip, et al., 2012). For example, reward-related cues that signal tasty foods or beverages automatically excite the motor cortex and bias go responses whereas cues associated with aversive tastes decrease motor excitability and bias no-go responses (Chiu et al. 2014; Gupta & Aron, 2011; Freeman et al., 2014; 2015). Thus, training go or no-go ('stop') responses to foods may in turn modify their associated hedonic and motivational value. This could arise from the creation of associative links between the foods and their associated go or no-go responses and two mutually inhibitory appetitive/aversive centers postulated by Dickinson and Dearing (1979; see Verbruggen et al., 2014a for a discussion). The link between stopping and aversion could explain why the value of stimuli associated with stopping and the consumption of no-go-related foods decreases.

Approach-avoidance training with alcoholic beverages as target stimuli on avoidance trials has also been associated with a devaluation of alcoholic beverages (e.g., Wiers et al., 2010; Wiers et al., 2011). Because this devaluation occurs in the absence of the inhibition of a motor response, it cannot be explained via the same mechanism outlined above. According to the evaluative coding account (Eder & Rothermund, 2008; Lavender & Hommel, 2007), devaluation of stimuli in the approach-avoidance training may occur because of the evaluative implications of the respond away and toward instructions. Away and toward response options may be assigned evaluative codes (i.e., respond away = negative, and respond toward = positive) that become associated with the trained stimuli through repeated association, eventually resulting in changes in valuation of the stimuli. A similar logic may apply to the dot-probe task, assuming that participants implicitly or explicitly code the responses as toward and away responses. Thus, different motor training tasks may produce changes in the value of trained stimuli, but do so via distinct mechanisms. It is also unclear to what degree changes in valuation influence attention (e.g., Anderson, et al., 2011; Schonberg, 2014a), or whether specific training paradigms (e.g., the dot-probe task) can have an effect on attention that is not mediated by a change in value. By extension, this theory suggests that repeatedly moving stimuli towards oneself, such as high-calorie foods or alcoholic drinks, may increase valuation of the stimuli in a manner that serves to sustain consumption. That is, the mere act of repeatedly consuming high-calorie foods and alcoholic drinks may drive increased valuation of them that maintains the behaviors and partially explains why weight loss and substance misuse treatments are often ineffective.

6.3 Modifying attention to food

Third, it has been theorized that some motor training procedures (indirectly) manipulate attention to food. In the dot-probe task, training responses toward low-calorie foods and away from high-calorie foods may *reduce* attention for the latter foods, which should reduce cravings for and intake of high-calorie foods (Kakoschke et al., 2014). A similar mechanism has been proposed in the domain of alcohol research (Field & Eastwood, 2005). This account is consistent with evidence that participants who completed dot-probe response-facilitation training showed reduced attentional bias for and intake of foods consistently not paired with the dot probe (Kakoschke et al., 2014; Kemps et al., 2014b). Changes in food choice after response-facilitation training have also been attributed to attention processes. Specifically, eye-tracking data suggest that people attend more to foods that have been subject to response-facilitation training during food choice tasks, and that this attention effect holds even for foods that are not chosen (Schonberg et al., 2014a). No studies have yet examined whether response-inhibition training and approach-avoidance training influence subsequent attention to food.

6.4 Rule-based learning

A fourth potential mechanism is that the training tasks lead to associatively-mediated activation of *abstract rule representations* (e.g. “if chocolate, then don’t go”), as opposed to direct changes in inhibition or motor circuitry. This theory states that during practice, foods can become associated with task goals (successful inhibition; moving away) or with the task rules that bias attention or action selection (e.g. look for a no-go signal and prepare for inhibition when chocolate is presented). After practice, the goal or rule representations may become automatically activated when the food is presented. This stimulus-rule association idea has not yet been directly examined in studies of food response training, however, it can be considered consistent with theories of automatic goal-priming and implicit self-control (e.g. Fujita, 2011).

Summary

In sum, four different mechanisms may account for the effectiveness of the different response training procedures. However, extant studies have not determined which of the above proposed mechanisms best accounts for the effects of food response training, as very few have examined these mechanisms as potential mediators of training effects on food intake, food choice, or weight loss. It should be noted that it is possible that all of these mechanisms are operating conjointly in some training procedures (i.e., they are not mutually exclusive). Specifically, response inhibition training may reduce food intake because it inhibits the motor system toward food and leads to lower valuations of high-calorie food. It may even decrease attention to food as a consequence of the devaluation, but this has not been tested. This combination may be unique compared to other interventions (e.g., in response-away training people still learn to respond to high-calorie food). It is important to determine which mechanism(s) mediate training effects, as interventions could then be further optimized to target these processes. Future studies should employ behavioral measures, eye-tracking, neuroimaging, and psychophysiology (fMRI, EEG, TMS and motor evoked potentials) to clarify which of the proposed mechanisms mediate training effects of different training procedures.

7. Pilot Test of a Multifaceted Food Response Training Treatment for Obesity and an Examination of the Mechanisms of Effect

Given the promising weight loss effects produced by food response training in the proof-of-concept trials involving the stop-signal and go/no-go trainings (Allom et al., 2015; Lawrence et al., 2015b; Veling et al., 2014), we conducted a pilot trial to evaluate the acceptability, feasibility, and efficacy of a more intensive and personally tailored multifaceted food response training treatment for obesity (Stice et al., 2016). This pilot trial also afforded an opportunity to advance knowledge on the mechanism of effect for response training among overweight/obese adults. We recruited 40 overweight/obese adults for a weight loss trial and randomly assigned them to a food response training condition or a parallel generic response training comparison condition involving non-food images.

In the food response inhibition training intervention participants completed 4 50-min weekly trainings during which they completed 5 training tasks. During each visit they completed 10-min versions of Veling's stop-signal training and Lawrence's go/no-go training in which low-calorie foods were used for go trials because this is the approach that Lawrence et al. (2015b) used in their response trainings that produced weight loss, and we thought acceptability would be higher if the intervention simultaneously trains response inhibition to high-calorie foods and response facilitation to low-calorie foods. We used 100% contingencies because the more strongly stimuli are associated with outcomes, the greater the associative learning. During each visit participants also completed a 10-min dot-probe response-facilitation training designed to directly train responses to low-calorie foods and indirectly inhibit responses to high-calorie foods, which have reduced attention for, choice of, and intake of high-calorie training foods (Kakoschke et al., 2014) and a 10-min respond-signal training in which participants pressed a button in response to a tone that accompanied the presentation of low calorie foods on 25% of the trials and withheld responding to high calorie food. During each lab visit they also completed a 10-min visual search training in which they quickly identified the one low-calorie food image in a larger array of high-calorie food images, as visual search training also appears to represent an effective response training strategy (Dandeneau et al., 2007).

Given that high-calorie food inhibition training is more effective when participants are hungry (Veling et al., 2013a,b), all trainings were conducted at least 3 hours since last caloric intake. To increase the likelihood that participants would complete all training sessions, we also prefaced training sessions with a brief motivational enhancement activity, which has been used to maximize compliance with efficacious obesity prevention programs (Stice, Rohde et al., 2012). For example, participants were asked to generate 5 health costs of obesity. All training tasks involved exposure to a broad range of commonly consumed high-calorie foods and beverages to maximize training generalizability. We tailored the high-calorie and low-calorie images of foods used in the training to the preferences of participants, as training effects were strongest for images of foods with the highest subjective palatability ratings (Schonberg et al., 2014a).

In the generic response-inhibition training control condition participants completed parallel response-inhibition and response-facilitation training with non-food images. This allowed us to tell participants that both interventions were designed to improve response inhibition, which should lead to weight loss given that impulsivity increases risk for overeating, ensuring credibility of the control intervention. We used 80 images of birds and 80 images of flowers (counterbalanced) for the control response-inhibition and response-facilitation training. We selected these categories to control for the visual complexity and intensity of food images used in the response training and to make training more engaging. This is a rigorous control condition, as it parallels the duration of the food response training intervention, with the exception that the inhibition training is generic, rather than food-specific. We decided to use a control condition in which participants completed a response-inhibition training task with non-food images because such training does not lead to any changes in caloric intake or weight (Guerrieri, Nederkoorn, & Jansen, 2012; Lawrence et al., 2015a, 2015b; Veling et al., 2014).

Participants showed excellent adherence (100%) to the training, reported high acceptability, and their training task performance data confirmed robust learning of stimulus-response associations (e.g. increasingly faster go reaction times to low-calorie foods).

Repeated-measures ANOVA models tested for group differences from pretest to posttest in percent body fat and palatability and monetary value ratings of food images. Models included intervention condition as a two-level predictor. Results showed significant condition x time differences in percent body fat ($F[1,38] = 7.64$, $p = .009$, $d = .90$) with 1.3% lower adjusted body fat at posttest for food response training participants relative to controls (43.1 vs. 44.4); this large effect translates into a 7% reduction in excess body fat. The effect size for this 4-hr intervention compares favorably to the average pre-post weight loss effect from more intensive 6-month behavioral weight loss treatments (d = .85; Franz et al., 2007) that are typically 50 hrs in duration over a 1-yr period. The effect size per hour of intervention is therefore a d = .23 (.90/4) versus a d=.02 (.85/50) for behavioral obesity treatment. Thus, our effect size is 12 times greater per hour of intervention than behavioral obesity treatment.

We also investigated the mechanism of action for the food response training. Intervention participants showed a larger attentional bias score for low-calorie foods over high-calorie foods and stronger respond-signal learning. Intervention participants also showed a significantly greater reduction in palatability and monetary value ratings of the high-calorie foods. There were significant condition x time differences in palatability ratings ($F[1,36] = 7.59$, $p = .009$, $d = .92$) and monetary value ratings ($F[1,36] = 7.57$, $p = .009$, $d = .92$) for unhealthy foods with food response training participants reporting lower palatability ratings at posttest (3.5 vs. 4.9) and lower monetary values (3.5 vs. 4.5) than controls. These data suggest that food response training reduces valuation in, and attention for, the high-calorie training foods, replicating the findings reviewed above.

In addition, fMRI analyses comparing the food response training and control participants on change in neural activity in response to high-calorie food picture > low-calorie food pictures showed significant group x time interactions in the right postcentral gyrus ($r = 0.73$), right mid insula (r's = 0.61 and 0.57), left superior temporal gyrus (r's = 0.72 and 0.61), bilateral Rolandic operculum (r left = 0.64; r right = 0.60), left inferior parietal lobe ($r = 0.66$), and right putamen ($r = 0.61$). The interactions revealed that the food response-training group showed significantly greater decreases in activity in brain regions implicated in attention (inferior parietal lobe), reward processing (putamen, mid insula), and sensory processing (postcentral gyrus, superior temporal gyrus), including oral somatosensory processing (Rolandic operculum) relative to changes observed in controls. Thus, results suggest that the food response training reduces attention- and reward-related responsivity to high-calorie foods, but provided little evidence of change in responsivity of inhibitory or motor regions.

8. Directions for Future Research

One important direction for future research is to develop more intensive response training interventions and evaluate their efficacy for reducing overeating and potentially other unhealthy appetitive behaviors (e.g., alcohol intake and substance use) in fully powered trials. Future research should test whether increasing the number of training sessions, the duration of training sessions, the frequency of training sessions, or adding booster trainings produce larger and more enduring intervention effects. Moreover, although our pilot trial of a longer duration response training treatment for obesity produced larger effect sizes than the briefer training interventions, providing evidence of a dose-response relation between training and the magnitude of intervention effects, it is possible that the implicit training rules from the different computer tasks did not harmonize. There might therefore be utility in using paradigms that have similar implicit training rules. For instance, the stop-signal and go/no-go response-inhibition training paradigms developed by Veling and Lawrence that produced weight loss appear to represent a useful starting point, as these directly train response inhibition to high-calorie foods and indirectly train response facilitation to alternative stimuli. A recent meta-analysis found that the degree to which participants were able to successfully inhibit responding on critical trials predicted larger effect sizes from response training interventions, but not the number of cue-specific inhibition trials or the contingency between appetitive cues and the requirement to inhibit a response (Jones et al., 2016). These data suggest that it would be best to maximize the number of successful inhibitions, but that training need not be overly long, which would reduce acceptability. One option to improve acceptability of more intensive training intervention would be to make the training more game-like (Jones et al., 2016).

Another important direction for future research would be to test whether adding food response training to standard obesity treatments, including behavioral weight loss interventions and bariatric surgery, increases the degree and duration of weight loss. There might also be utility in testing whether food response training might prove useful in the prevention of excess weight gain, either alone or in combination with evidence-based obesity treatment interventions.

A third important direction for future research would be to examine the mechanisms of effect for response training, including a test of whether the various response training approaches discussed herein involve similar or distinct mechanisms of effects. Based on our pilot trial, functional brain imaging appears to represent a useful tool for this endeavor because it allows a simultaneous test of whether training results in changes in the responsivity of brain regions that theoretically occur for the distinct mechanisms of effect. Greater pre-to-post decreases in responsivity of reward valuation regions (e.g., orbitofrontal cortex, caudate, amygdala) to images of high-calorie foods in participants who complete response training relative to changes observed in control participants would be consistent with a reward valuation mechanism of effect. Greater increases in responsivity of inhibitory regions (e.g., ventrolateral and dorsolateral prefrontal regions) to images of high-calorie foods in participants who complete response training relative to changes observed in control participants would be consistent with changes in inhibitory control. Greater decreases in responsivity of attention regions (e.g., anterior cingulate cortex and visual occipital cortex) to high-calorie food images would be consistent with changes in attention, and greater decreases in responsivity of motor regions (e.g., supplementary motor area) to high-calorie foods would be consistent with rule-based learning accounts. Figure 2 summarizes how these putative mechanisms may map onto neural regions and associated behavioral measures to provide a framework for future research.

A fourth direction for research would be to investigate factors that amplify the effects of response training interventions, which would allow interventionists to target the populations most likely to benefit from this new therapeutic modality. As the strength of the inhibitory effect of stop signals is theoretically a function of the strength of the initial approach impulse (Nakata et al., 2006), response training should be most effective in inhibiting high-calorie food intake for those with a strong innate approach response to such foods, such as those with elevated scores on reward sensitivity measures. The effects of a short-term response-inhibition training on acute consumption of training versus non-training foods was indeed greater for those with high versus low BMI (Veling et al., 2011) and a 4-week response inhibition training produced significant weight loss for overweight and obese dieters, but not for dieters with a healthy weight (Veling et al., 2014). Response-inhibition training also produced stronger reductions in high-calorie food intake for participants at risk for overeating by virtue of elevated impulsivity (Houben, 2011); individuals with inhibitory control deficits show greater future weight gain (Seeyave et al., 2009; Sutin et al., 2011). Similarly, the effect of response-inhibition training on slowing the speed of a button press in response to training versus non-training foods and on reducing consumption of training versus non-training foods was greater for participants at risk for overeating by virtue of high dietary restraint (Houben & Jansen, 2011; Lawrence et al., 2015a; Veling et al., 2011); individuals with higher dietary restraint scores show greater future weight gain (Dong et al., 2015; Field et al., 2003; Stice et al., 1999). It might also be interesting to test whether the effect of response training is moderated by participant age, given evidence that the development of reward circuitry peaks earlier than the development of inhibitory circuitry (Gogtay et al., 2004; Ernst, Pine, & Hardin, 2006). Given the evidence reviewed previously that a key mechanism of effect of response training occurs through reductions in overvaluation of high-calorie foods, it is possible that food response training will be more effective in adolescence and adulthood, rather than in childhood, when reward circuitry is still developing. Because response training did not seem to affect responsivity of inhibitory regions in our pilot trial, it is unclear whether development of that circuitry would moderate the effects of this intervention.

There may also be utility in testing the hypothesis that food response training will be more effective for participants with a genetic propensity for greater dopamine signaling capacity in reward circuitry, as reflected by a multilocus score, based on evidence that such individuals show elevated reward region response (Nikolova et al., 2011; Stice, Yokum et al., 2012) and weight gain in three samples (Yokum et al., 2014). This multilocus score reflects the number of genotypes possessed by each participant that have been associated with greater dopamine signaling, including the *TaqIA* A2 allele, *DRD2*-141C Ins/Del and Del/Del genotypes, *DRD4*-S allele, *DAT1* 9R allele, and *COMT* Val/Val genotype. It might also be useful to test the novel hypothesis that the effects of the response training on weight loss will be significantly stronger for participants who show greater responsivity of reward regions (e.g., orbitofrontal cortex, striatum, amygdala) and attention (anterior cingulate, occipital cortex), and weaker responsivity of prefrontal inhibitory regions (dlPFC, vlPFC) to images of high-calorie food images versus low-calorie foods or control stimuli (e.g., glasses of water) at pretest. Research has not tested whether directly measured hyper-responsivity of reward and attention regions and hyporesponsivity of inhibitory regions predicts greater efficacy of response training. It is possible that the moderating factors described above (elevated BMI, impulsivity, and dietary restraint) are proxy markers for these neural vulnerability factors; obese versus lean individuals and those with high versus low dietary restraint scores show greater reward region response and reduced inhibitory region response to high-calorie foods (e.g., Batterink et al., 2010; Burger & Stice, 2011; Gearhardt et al., 2014; Stoeckel et al., 2008).

9. Conclusions

In sum, brain imaging studies have revealed that obese versus lean individuals show greater activation of reward and attention regions and reduced activation of inhibitory regions in response to food cues, and further that individuals who show greater reward and attention response and lower inhibitory region response exhibit elevated future weight gain. These data imply that an intervention that reduces reward and attention region response to food cues and increases inhibitory region response might prove useful in the treatment of obesity. Critically, emerging findings from basic science suggest that training individuals to inhibit motor responses to high-calorie foods via computerized tasks resulted in weight loss in four independent trials. It would be useful for future research to evaluate more intensive food response training interventions for the treatment of obesity in adequately powered trials and to determine whether they produce lasting weight loss among overweight and obese individuals. There may also be utility in evaluating whether adding such a food response training intervention to extant weight loss interventions increases their efficacy, particularly given the low expense of response training. With continued refinement, response training may come to represent a powerful clinical tool for addressing the morbidity and mortality associated with excess body weight.

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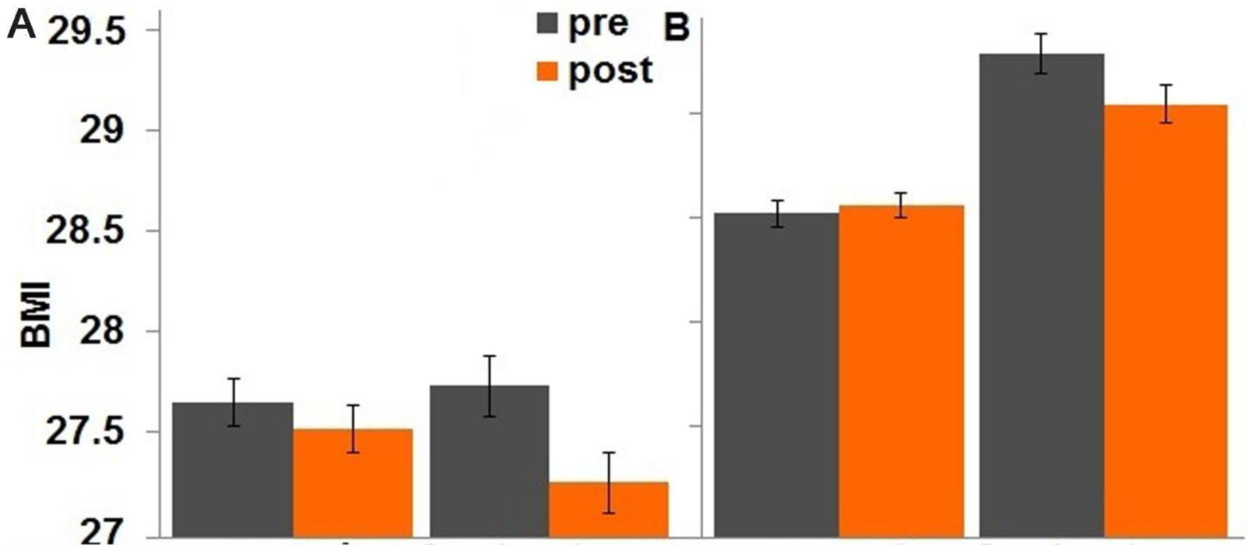
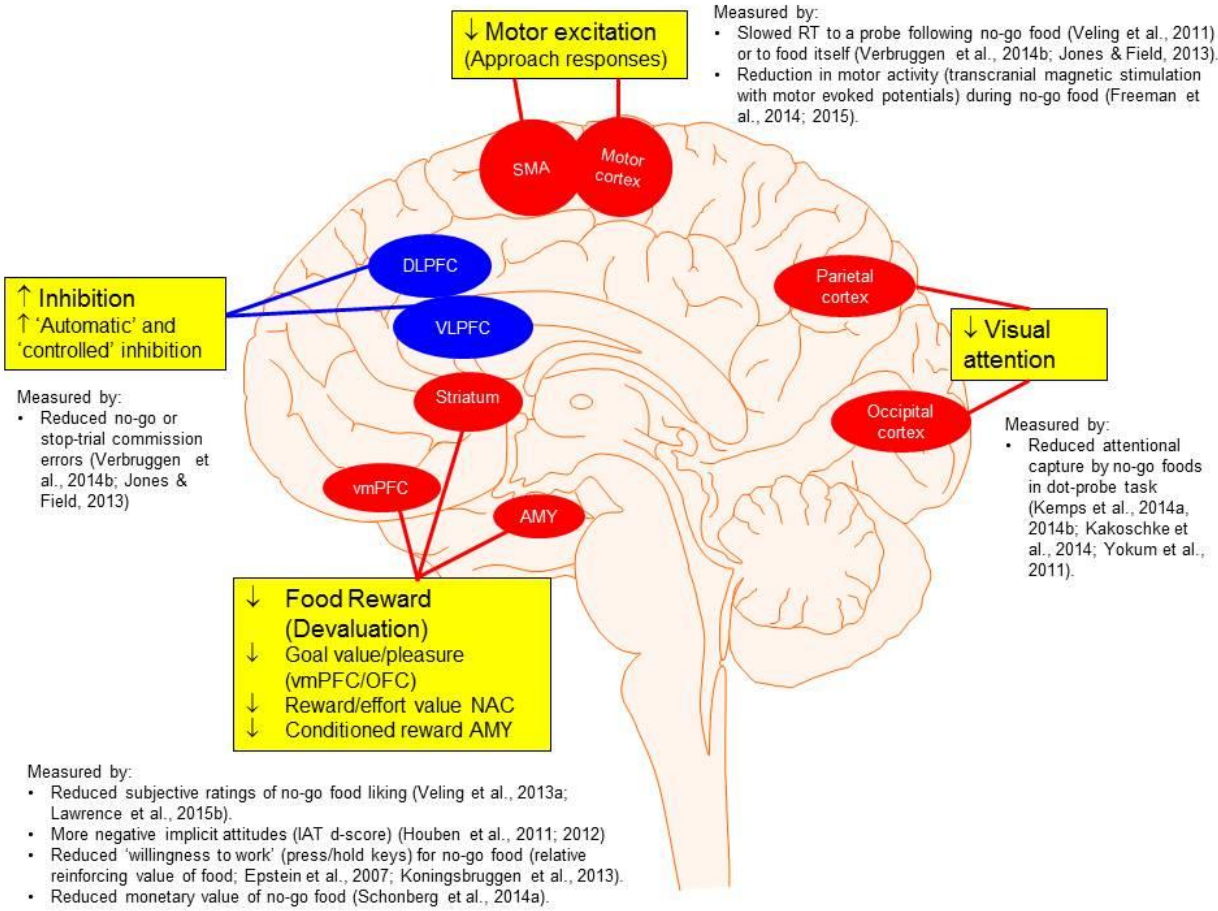
Figure captions

Figure 1. Body mass index at pre- and post-intervention as a function of go/no-go condition in A) the subset of overweight/obese individuals from Veling et al. (2014) and B) All participants (lean to obese, on average overweight, individuals recruited from the community) from Lawrence et al. (2015b).

Figure 2. Schematic of brain regions and associated mechanisms involved in overeating that we propose could be modified by food response inhibition training. Red colors indicate reward-, attention- and motor approach-related brain regions positively associated with BMI and food intake; blue colors indicate regions involved in inhibitory control, which are negatively associated with BMI and food intake. We hypothesize that food response inhibition training could modify all of these neural mechanisms (see text). Please note this is a simplified figure constructed for heuristic purposes that only shows key replicated neuroimaging findings to date. "Striatum" includes nucleus accumbens, putamen and caudate regions, and "vmPFC" includes orbitofrontal cortex regions implicated in previous fMRI studies. The insula and somatosensory (taste) cortex are also involved in processing food reward but have been less consistently linked to overeating and are omitted from this schematic for simplicity.


A
B
pre
post
BMI
29.5
29
28.5
28
27.5
27


↓ Motor excitation
(Approach responses)
Measured by:
• Slowed RT to a probe following no-go food (Veling et al., 2011) or to food itself (Verbruggen et al., 2014b; Jones & Field, 2013).
• Reduction in motor activity (transcranial magnetic stimulation with motor evoked potentials) during no-go food (Freeman et al., 2014; 2015).
SMA
Motor cortex
DLPFC
VLPFC
↑ Inhibition
↑ 'Automatic' and 'controlled' inhibition
Measured by:
• Reduced no-go or stop-trial commission errors (Verbruggen et al., 2014b; Jones & Field, 2013)
Parietal cortex
↓ Visual attention
Occipital cortex
Measured by:
• Reduced attentional capture by no-go foods in dot-probe task (Kemps et al., 2014a, 2014b; Kakoschke et al., 2014; Yokum et al., 2011).
Striatum
vmPFC
AMY
↓ Food Reward (Devaluation)
↓ Goal value/pleasure (vmPFC/OFC)
↓ Reward/effort value NAC
↓ Conditioned reward AMY
Measured by:
• Reduced subjective ratings of no-go food liking (Veling et al., 2013a; Lawrence et al., 2015b).
• More negative implicit attitudes (IAT d-score) (Houben et al., 2011; 2012)
• Reduced 'willingness to work' (press/hold keys) for no-go food (relative reinforcing value of food; Epstein et al., 2007; Koningsbruggen et al., 2013).
• Reduced monetary value of no-go food (Schonberg et al., 2014a).