Published in final edited form as:

Curr Psychiatry Rep. 2017 September ; 19(9): 62. doi:10.1007/s11920-017-0813-7.

Neurocognitive Treatments for Eating Disorders and Obesity

Dawn M. Eichen, Ph.D.^{1,*}, Brittany E. Matheson, M.S.^{1,2}, Sara L. Appleton-Knapp, Ph.D.¹, and Kerri N. Boutelle, Ph.D.¹

¹Department of Pediatrics, University of California San Diego, La Jolla, California

²San Diego State University/University of California, San Diego

Abstract

Purpose of Review—Recent research has highlighted executive function and neurocognitive deficits among individuals with eating and weight disorders, identifying a potential target for treatment. Treatments targeting executive function for eating and weight disorders are emerging. This review aims to summarize the recent literature evaluating neurocognitive/executive function-oriented treatments for eating and weight disorders and highlights additional work needed in this area.

Recent Findings—Cognitive remediation therapy (CRT) for anorexia nervosa has been the most extensively studied neurocognitive treatment for eating disorders. Results demonstrate that CRT improves executive function and may aid in the reduction of eating disorder symptomatology. Computer training programs targeting modifying attention and increasing inhibition are targeting reduction of binge eating and weight loss with modest success.

Summary—Neurocognitive treatments are emerging and show initial promise for eating and weight disorders. Further research is necessary to determine whether these treatments can be used as stand-alone treatments or whether they need to be used as an adjunct to or in conjunction with other evidence-based treatments to improve outcomes.

Keywords

Eating Disorders; Obesity; Executive Function; Neurocognitive Treatment

Introduction

In the United States, roughly 4.4% of adults have some form of eating disorder(1), and two thirds of adults have obesity or are overweight (2). Although evidence-based treatments exist for these disorders, remission is not achieved for nearly half of individuals in treatment (3,

*Corresponding Author Contact: deichen@ucsd.edu, Dawn Eichen, 9500 Gilman Dr, MC0874, La Jolla CA, 92093.

Compliance with Ethics Guidelines

Conflict of Interest

Dawn M. Eichen and Brittany E. Matheson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

4), recidivism is common (5, 6) and treatment dropout rates are high (6, 7). There is a pressing need to identify and target underlying mechanisms to improve treatment outcomes.

Growing research suggests executive function deficits exist across eating and weight disorders; however, evidence-based treatments do not currently target these mechanisms. Neurocognitive and executive function-oriented treatments are emerging for eating and weight disorders and show initial promise. This area is still in its nascent stages but this review aims to 1) briefly review the neurocognitive deficits among eating and weight disorders, 2) summarize the research evaluating the efficacy of neurocognitive treatments of eating and weight disorders, and 3) discuss future steps needed for research in this area. Together, this review will serve to evaluate the state of neurocognitive treatments for eating and weight disorders and will highlight the importance of targeting these mechanisms in treatment. To assist readers this review is organized by diagnosis and the evidence describing neurocognitive deficits and neurocognitive treatments are presented separately for each diagnosis.

Brief Overview of Neurocognitive Deficits in Eating and Weight Disorders

Research suggests that individuals with eating and weight disorders display executive function impairments compared to individuals without these disorders (8, 9). Executive function or cognitive control broadly refers to top-down mental processes that enable effortful control over behavior. Executive functions include inhibitory control (i.e., attention control, self control), working memory, and cognitive flexibility that feed into higher level executive functions such as reasoning and problem solving (10). Executive function plays a strong role in regulating eating behavior and related thoughts and impairments in these areas are associated with dysfunction found in eating and weight disorders. A good framework for understanding these neurobiological differences is the “core eating network” proposed by Chen et al. (11). This neural model outlines a dorsal control pathway and a ventral reward pathway in the brain that modulate food consumption (11). The imbalance of these networks present as impairments in executive function ranging from over-controlled/rigidity (i.e., low reward, high inhibition) to under-controlled/disinhibited (i.e., high reward, low inhibition). The range of executive function impairments maps onto the spectrum of eating and weight disorders, with individuals with anorexia nervosa (AN) exhibiting more over-controlled tendencies where as individuals with binge-eating disorder (BED) or overweight/obesity (OW/OB) exhibiting more under-controlled tendencies. Details regarding the specific neurocognitive impairments exhibited by each disorder are described below.

Anorexia Nervosa

Typically, individuals with AN show impairment in the areas of cognitive flexibility and decision making (12). Individuals with AN exhibit imbalance in the ventral limbic and dorsal executive circuits which are implicated in inhibition, decision making and reward response (13). This imbalance may lead individuals with AN to modulate their responses to hedonically appealing foods based on pre-defined rules rather than reward drive or hunger state. For example, these neurobiological-based differences may allow individuals with AN to maintain low caloric intake through strict adherence to a system of rules about what to eat

and what not to eat, even in the presence of highly palatable, energy-dense foods. Behavioral research findings support these differences in decision-making, as individuals with AN make poorer decisions than healthy controls (HCs; i.e., individuals within the normal body weight BMI range and do not have an eating disorder) on the Iowa Gambling Task, a task in which individuals incorporate past experience into future decision making (14). Similarly, research also suggests that individuals with AN demonstrate the ability to delay rewards, as measured by delay discounting tasks, compared to HC's in tasks involving non-food rewards (15, 16). A study utilizing fMRI compared performance on a delay discounting task for women in recovery from AN to HCs across metabolic states (fasted versus sated), finding increased activation in cognitive control brain regions for HCs when sated but no differences in these areas for women in recovery from AN in either state (17). Taken together, these findings suggest that individuals with AN may be particularly good at delaying short-term rewards in favor of long-term gains, regardless of hunger status, which could have implications for eating and exercise behaviors.

Furthermore, individuals with AN perform worse on set-shifting tasks such as the Wisconsin Card Sorting Test or the Trail Making Test compared to HCs. This can translate into rigidity, making it difficult for them to change the rules and rituals related to food consumption that maintain AN (18). Central coherence – or difficulty seeing the forest through the trees – refers to the ability to consolidate individual objects or pieces of information into a larger, holistic picture or construct. A meta-analysis shows that individuals with AN perform poorly on tests of central coherence such as the Group/Embedded Figures Test or Rey-Osterrieth Complex Figure Test compared to HCs (19). Weak central coherence could help maintain AN symptomatology as it may cause individuals with AN to focus more on the details of their weight or shape and not on the bigger picture of their overall health (18).

Bulimia Nervosa—Impairments in inhibitory control are found among individuals with bulimia nervosa (BN), particular when examining stimuli related to the disorder (e.g., food, body shape) (20). Moreover, impairments in decision making are associated with BN compared to HCs. For example, a study investigating temporal discounting found that adults with BN placed less value on future rewards than HCs, a characteristic which may make them more susceptible to binge eating (21). Another study examined executive function (composite Z-score combining measures of set-shifting, problem solving and inhibition) in those diagnosed with BN or AN and compared them to HCs. This study found that although both the BN and AN groups showed impaired executive function compared to HCs, individuals with AN performed significantly worse than those with BN (22). These results are consistent with those of another study that compared patients with BN alone and patients with BN and a previous AN diagnosis to HCs. The former study found that patients with a dual diagnosis performed worse on set-shifting and on decision-making tasks than those diagnosed only with BN. A meta-analysis on central coherence suggests that individuals with BN show significantly weaker central coherence on some measures (19). These results suggest that although some executive functioning deficits are similar in these two disorders, AN can result in more severe impairment in some domains (23). However, individuals with BN may be more impulsive – particularly in regards to eating behaviors – such that deficits in inhibitory control processes may be contributing to the maintenance of disordered eating

behaviors/binge episodes. Individuals with BN show hypoactivity in the anterior cingulate region and parahippocampal regions when compared to HCs during a task examining re-orienting attention and executive control of attention (24). This hypoactivity during reorienting may explain why individuals with BN have difficulties with preoccupations about thoughts about food and body image while the hypoactivity during executive control is related to impairments in inhibition (24). A review of the neurobiological mechanisms of individuals with AN and BN show altered activity of dorsal circuits (25) which could lead to the higher inhibition in those with, AN and lower inhibition in those with BN that has been demonstrated in behavioral tasks.

Binge-Eating Disorder—Unlike those with BN, individuals with BED perform worse than individuals with AN on decision-making, cognitive flexibility, and central coherence (12). While many individuals with BED have comorbid OW/OB which also influences neurocognitive functioning (see next paragraph), their neurocognitive profile differs from that of people with OW/OB who do not binge eat. It is possible that OW/OB compounds the neurocognitive changes seen with BED. Specifically, people with OW/OB and BED perform worse on tasks that measure self-regulatory control, planning, and working memory than do people with OW/OB without BED (26). With regard to inhibitory control, both of these groups show deficits in general inhibitory control when compared to HCs, but do not differ from each other (27). However, individuals with BED and obesity exhibit more food-related impulsivity than do those with obesity without BED (27). Although fewer neuroimaging studies exist for BED, a review of the research suggests that individuals with BED exhibit altered responses found in corticostriatal circuitry which are related to processing motivation/reward and impulsivity (28). Specifically, individuals with BED show increased activity in the dorsal anterior cingulate cortex in response to high calorie food cues compared to those without BED (29), suggesting or contributing to loss of control over the consumption of these foods. Adults with OW/OB and BED show less activity in the prefrontal cortex (i.e. area implicated in inhibitory control) than do those with obesity alone (27).

Overweight/Obesity—Interestingly, OW/OB in the absence of EDs is also associated with neurocognitive deficits. (19, 30, 31) Increased BMI is associated with higher levels of impulsivity, although debate exists as to whether the impulsivity is primarily food-related or generally impaired (32). Individuals with OW/OB exhibit impaired decision-making and central coherence compared to HCs, but evidence for reduced cognitive flexibility is mixed (33). It should be noted that in studies that demonstrate a relationship between OW/OB and impaired decision-making and central coherence do not all control for comorbidities to obesity, such as cardiovascular disease or depression, that could potentially explain the relationship (33). To date, there does not appear to be a relationship between the level of executive function impairment and degree of obesity (34). Individuals with OW/OB without BED show more activation in the orbitofrontal cortex, amygdala, ventral striatum, and the anterior cingulate cortex, or “reward pathway” than HCs in response to food cues (11). Moreover, increased weight is associated with decreased activation in the inhibitory control regions (e.g., prefrontal cortex) while completing a behavioral impulsivity task with food stimuli (11). Taken together, overeating and subsequent weight gain may result from

impaired reward processing that leads to greater consumption of calorically-dense, hedonically-pleasing food coupled with decreased inhibition to resist consumption (11).

Treatments Targeting Neurocognitive or Executive Function in Eating and Weight Disorders

Despite evidence suggesting that executive function deficits exist across a range of eating and weight disorder diagnoses (9, 19, 30, 35), current evidence-based treatments do not specifically target these processes. For example, cognitive behavioral therapy targets normalizing eating patterns and addressing cognitive distortions, dialectical behavior therapy targets underlying emotion dysregulation, and behavioral weight loss targets reducing calories consumed and increasing physical activity. Altogether, an understanding of the neurocognitive differences across eating and weight disorders can be leveraged to form the basis of treatments specifically targeted to a particular disorder. Further development of treatments targeting these underlying mechanisms, which can improve neurocognitive functioning for individuals with eating and weight disorders is needed (36–38). With low remission and high recidivism rates in current treatment modalities (3–7), it is important to investigate adjunctive or alternative treatments that target these underlying mechanisms.

Anorexia Nervosa

Cognitive Remediation Therapy—Cognitive remediation therapy consists of in-session cognitive exercises that encourage individuals to reflect upon their own cognitive style to gain awareness of their thinking processes to encourage more adaptive thinking styles and the application of these skills to real-life situations. CRT targets the development of a more holistic and flexible thinking style and encourages more flexibility in every day behaviors. CRT is thought to target cognitive processes such as set-shifting and central coherence that are known to be deficits associated with AN symptomatology (39). Instead of focusing on eating disorder symptoms directly, CRT works on increasing overall cognitive flexibility through a series of exercises designed to present alternative thinking styles and reduce cognitive rigidity (37). CRT is most commonly delivered in person over 8–10 weekly sessions, though studies report that CRT is acceptable and feasible in individual, group, and computerized formats (40–44). CRT has been applied to improve cognitive functioning in populations such as traumatic brain injury and schizophrenia, and has also been adapted for depression (45–48). In AN, CRT is typically used as an adjunctive intervention to supplement evidence-based treatment in order to bolster retention while simultaneously improving cognitive flexibility to maximize treatment outcomes (37, 43, 49).

Systematic reviews indicate that CRT improves set-shifting and central coherence for patients with AN (43, 50). Across studies, analyses reveal medium to large effect sizes in terms of improved neurocognitive performance following CRT across a variety of standardized neuropsychological assessments (37). To date, four randomized controlled clinical trials on CRT for adults with AN have been completed, with promising results of not only improved set-shifting but also reduced eating disorder symptoms (40, 50–53). However, it can be hard to compare results across RCT's as the methodological designs, patient populations, and CRT treatment formats vary across studies.

CRT has also been applied among children and adolescents with AN, with somewhat more mixed results than adult samples. A within-subjects design showed that significant improvements on neurocognitive measures were found in a child and adolescent inpatient population with AN after undergoing an eight-session CRT program (54). Compared to HCs, adolescents with AN (n=20) demonstrated improved cognitive flexibility on neuropsychological measures following CRT, although improvements in self-reported flexibility (as measured by the Cognitive Shift and Behavioral Shift subscales of the Behavioral Rating Inventory for Executive Functioning, BRIEF-SR) and central coherence (as measured by copy condition of the Rey-Osterrieth Complex Figure Test) did not differ between the two groups (55). Although no empirical data were reported, a small sample of inpatient adolescents with AN found a group-based CRT program to be fun, playful, and engaging (56). Adolescents in a day treatment program reported some improvement in self-reported cognitive flexibility following a group-based CRT program (57). However, a recent meta-analysis found limited support for set-shifting difficulties in children and adolescents with AN compared to HCs (58). The lack of set-shifting difficulties in children with AN compared to HCs may be due to these mechanisms not being as well-developed in normal children at this age or perhaps that the difficulties found in adults with AN may be the result of chronic starvation and illness duration. Thus, it is important to explore whether CRT for children and adolescents with AN may have less utility than for adults or if perhaps it can be advantageous and aid in the development of adaptive cognitive functioning.

While CRT offers many potential benefits as an adjunctive treatment with adults, the current state of the literature presents several limitations. As noted by others, CRT is often conducted in inpatient populations, with small samples and limited statistical power, with severely limits the generalizability of the results (36, 43). Despite these limitations, CRT has many potential benefits, including increased motivation and treatment adherence (50). In particular, high treatment drop-out rates in outpatient treatments are observed in eating disorder populations (6), likely due to both the intensive nature of treatment and the ego-syntonic symptomatology that characterizes the disorder, in particular AN. Thus, CRT may offer additional benefits in terms of treatment outcomes above and beyond any improvements in executive functioning. Overall, the current state of the evidence suggests that CRT may be acceptable and effective as an adjunctive treatment for AN, though more research with a greater emphasis on longitudinal outcomes in this area is warranted.

Bulimia Nervosa

Computerized Video Games—Compared to AN, much less is known about the utility of executive function treatments for BN. BN is thought to be a disorder of under-regulated impulse control (25). Thus, executive function treatments designed to target inhibition, impulsivity, and emotional regulation may be especially beneficial for improving these areas within this population. One study utilized a computerized video game to train emotion regulation and impulse control as an adjunct to traditional Cognitive Behavioral Therapy for individuals with a bulimic-type of eating disorder (defined as BN, BED, or ED-NOS)(59). This study noted improvements in emotion regulation (as measured via psychophysiological and self-reported reductions in anxiety) as well as reductions in both binge and vomiting episodes (59). However, the study sample was extremely small (nine individuals) and had

varying diagnoses and symptom presentation; thus, the study's findings may not be generalizable and further replication in larger treatment samples is warranted before meaningful conclusions can be drawn. A single case study also utilized a computerized videogame to enhance inhibitory control prior to engaging in CBT for one patient with BN and reported within-subject decreases in impulsivity as well as binge episodes (60). Despite small sample sizes, these studies provide initial evidence for the potential efficacy of a computerized training program aimed at targeted core components of executive functioning and cognitive control which may supplement existing evidence-based treatments for eating disorders.

Binge-Eating Disorder

Attention Modification and Inhibitory Control—Neurocognitive treatments may also play an important role in BED. The imbalance between salient, bottom-up reward processes that promote overeating and top-down inhibitory control processes that seek to limit food consumption may be one contributing factor in overeating and binge eating (61, 62). More recently, treatments targeting overeating and weight gain have started to include components aimed at neurocognitive processes related to inhibition, impulsivity, and attentional bias. Attention bias modification programs, originally developed for use in anxiety disorders (63), may be a promising intervention to treat disordered eating (64). By training one's automatic attention away from food, the need to utilize impaired top-down inhibitory control processes over eating behavior is limited; thus, in theory, attention modification training may help prevent disinhibited eating. An initial, open-label, pilot study of an eight-week attention bias modification program for overweight adults with binge eating appears to be effective in decreasing binge episode frequency as well as producing modest weight-loss outcomes within subjects (65). Food-specific anti-saccade training may also provide added benefit in decreasing impulsivity as well as training attentional bias away from highly salient food cues in populations with BED (66, 67). A small proof of concept RCT that randomized 22 females with DSM-5 BED to either a 3-session anti-saccade training condition (look away from high calorie food picture shown) or a control (gaze wherever you would like) showed that both conditions reduced self-reported binges in the four weeks following the training (68). RCTs are currently underway that specifically focus on decreasing impulsivity among individuals with BED (69). Additional studies that investigate the use of attention bias modification and inhibitory control training programs should be conducted in eating disorder populations in order to determine the utility of this implicit, computerized treatment in reducing eating disorder symptomatology.

Overweight and Obesity

The relation between OW/OB and cognitive function is still being explored. As stated above, significant evidence shows that neurocognitive deficits are related to OW/OB. However, a recent meta-analysis demonstrated improvements in neurocognitive function following weight loss among adults (70). Further, baseline executive function levels may moderate treatment response. Specifically, executive function was found to moderate treatment response in a weight-loss trial for African American adolescents, such that adolescents with higher executive function lost more weight than those with lower executive function (71). Taken together, it is possible that a bi-directional relationship may exist such that poor

executive function can lead to increased weight and decreases in weight can improve executive function. Given this, several studies have begun to examine whether targeting executive function as part of treatment can be effective for weight loss. A RCT utilizing self-regulation strategies effectively reduced weight gain in a large sample (n=599) of young adults (72). Several RCT's utilizing executive function training for obesity are currently underway, including a RCT comparing computerized self-regulation training for obese adolescents (compared to a placebo condition) (73) as well as RCTs using manualized CRT for adult weight loss (74, 75). While the field has recognized the potential of targeting EF in the context of weight-loss interventions (30, 31, 76), additional research is needed to better understand the relationship between EF and the short and long-term maintenance of weight loss.

Physical Activity Interventions—Research suggests that OW/OB are related to executive function deficits in children and adults (30, 31). Physical activity, which has been related to executive function, is an important component of weight loss treatments. A systematic review highlighted that physical activity interventions may promote greater cognitive benefits among OW/OB children and adolescents compared to normal weight peers while acknowledging some limitations with the current research (77). OW/OB adolescents randomized to a competitive physically active videogame not only improved in executive functioning skills significantly more than adolescents in either the cooperative videogame and control group conditions, but this improvement in executive functioning was also positively correlated with weight loss following the ten-week intervention (78).

Computerized Inhibitory Training: Research suggests that training inhibitory control processes while reducing attentional and salient reward responses to food cues may provide an effective treatment target to reduce overeating and weight gain (38, 79). Obese children in an inpatient treatment program randomized to a six-week executive function computerized training condition targeting inhibition and working memory showed greater improvements in working memory and maintained their weight loss compared to children in the treatment as usual condition (80). OW/OB adults that were assigned to an active response inhibition training (Go/No-Go computer task) lost more weight and rated liking and attractiveness of food lower than adults assigned to a control condition (81). Adult dieters who participated in four brief Go/No-Go computer trainings with the No-Go trials associated 100% for high-calorie food and beverage images lost more weight than those trained with non-food images with stronger effects found for those with a greater BMI (82) signifying the potential for this intervention to aid weight loss. Several laboratory studies have examined a variety of tasks (dot-probe, Go/No-Go, Stop Signal) and have shown that brief computerized trainings may have an impact on cognitive function and immediate food consumption in the laboratory (83–85). A recent meta-analysis examined inhibitory control trainings for appetitive behaviors (food and alcohol) found a small but significant effect compared to control treatments (86). Although typically these studies have used university or non-overweight adults, they highlight the need to better explore these trainings for the potential to aid weight loss and reduce binge eating.

Another proposed avenue for reducing overeating and weight gain is to target learned responses to highly salient food cues that promote eating in the absence of hunger (87–89). These programs have shown preliminary efficacy, and are thought to strengthen motor inhibition. Overall, preliminary work in targeting executive function in overweight and obesity appears to offer promising results in terms of improved neurocognitive functioning as well as modest weight-loss outcomes that deserve further attention and research.

Directions for Future Research: There is sufficient evidence to suggest that neurocognitive impairments exist among individuals with eating and weight disorders. Research examining the potential of targeting these deficits in treatment of eating and weight disorders is nascent. However, it is important to evaluate these alternative mechanisms to target in treatment due to the necessity to improve dismal treatment outcomes for these conditions.

Anecdotally, when treating patients with eating and weight disorders, it is apparent how these neurocognitive deficits interfere with treatment outcome. Patients with AN are rigid and cannot fathom giving up their specific food and eating rules. Utilizing a treatment that does not directly target the eating behaviors such as CRT may be particularly useful in helping to reduce treatment dropout by allowing the patient to engage in treatment without having to directly address eating disorder pathology. As cognitive flexibility improves, it may be easier to engage the patient in directly addressing the eating disorder symptoms through other evidence-based approaches for AN. Further, computerized training should be explored to see whether training implicit mechanisms could be useful in targeting eating disorder pathology. For example, computerized trainings that use implicit mechanisms to target deficits in executive functions may be able to improve these areas in order to influence behaviors and indirectly promote treatment success. Moreover, patients may be more willing to comply with treatments that don't explicitly target eating disorder symptoms. If these programs can boost the effects of treatment, they could be a cost-effective way to do so.

Patients who experience loss of control (i.e., BN, BED) over eating report substantial distress over this loss of control. Weight-loss treatments require high amounts of effortful control and patients with low inhibition struggle. If inhibitory training could aid in reducing this loss of control or need for effortful control, or if attentional training can strengthen automatic processes and reduce the need to utilize inhibitory control, this could drastically reduce loss of control or overeating. Further, unlike the current evidence-based treatments which largely require in-person meetings for a significant amount of time, computerized trainings would be a less expensive alternative or adjunct, are easily disseminable, and can be completed at home at any time of day without needing a professional to administer it. Moreover, utilizing hand-held technology, such as smartphone or internet-based applications, may provide greater dissemination of these resources, allowing individuals to access training and support from a mobile device in real-time.

Although initial evidence is promising for neurocognitive treatments, significant limitations exist with the current research reviewed. The majority of research examining treatments targeting neurocognitive function is preliminary efficacy/proof-of-concept pilot studies. As such, they have small sample sizes and have often utilized specific populations (e.g., inpatient, predominantly female) which may impact generalizability. Thus, while promising,

these findings must be interpreted with caution and should inspire more rigorous trials. Further, it is important to explore whether any of these treatments, like CRT could be applied transdiagnostically. One study included a few patients with BN, while exploring the impact of adding CRT to treatment as usual for patients with severe and enduring eating disorders (53). This study found no moderating effects as to whether patients had restrictive vs binge-purge symptomatology, suggesting there may be transdiagnostic applications. Further, studies are undergoing that have modified CRT to apply to the neurocognitive deficits found among OW/OB and are currently testing its effects (74, 75). Computerized trainings produce favorable effects, particularly when comparing the limited amount of time they have typically been deployed to time-intensive behavioral interventions (38); however, it is unknown whether these interventions could succeed long term as stand-alone treatments and this must be evaluated in future research. Relatedly, rigorous research examining the dose of treatment needed for withstanding effects to help tease apart whether computerized trainings need to be consistently utilized or perhaps if booster sessions could be deployed when effects begin to disappear is needed. Further, research examining the mechanisms by which these neurocognitive treatments are effective can help increase potency of the treatment. Lastly, exploration as to whether these treatments should be targeted at individuals who may benefit the most (i.e., demonstrate greatest deficits) would be informative.

To date, more research has examined neurocognitive treatments in adults. In CRT, the effects need to be better understood in children and adolescents as developmental considerations are needed. Areas of the brain implicated in executive function develop into young adulthood (90). Thus, it is important to understand whether treatments targeting these areas can help shape the development of executive function in children adolescents or whether these treatments are more effective once the brain is developed and target re-wiring the already developed brain. It is possible that one explanation for the limited effectiveness of CRT in children and adolescents is that these areas have not yet been developed and the treatment may not be as effective. Alternatively, it may be important to utilize these treatments to help encourage positive neurocognitive development. Regardless, when targeting children, it may be necessary to consider age and cognitive development. Further, it is important to not only consider whether change in cognitive function is seen following these treatments, but it is necessary to understand how the measured cognitive change is related to neurobiological changes measured through techniques like neuroimaging (e.g., activation, network connectivity). Research should continue examine and utilize neurobiological evidence to help identify additional treatment targets for eating and weight disorders. In addition to other behavioral treatments that can be developed to address these neurocognitive deficits, this research could potentially illuminate future pharmacological targets.

Conclusion

In conclusion, neurocognitive deficits occur across eating and weight disorders. Targeting these deficits has strong potential at enhancing existing treatments, and could potentially reduce recidivism rates. Additional research is needed to better understand their utility and to help maximize the impact they can have. Further, as we move away from a “one size fits all” approach to treatment, these treatments may allow for us to characterize neurocognitive

profiles and individualize treatments to target the specific neurocognitive deficits seen. This field is advancing rapidly and it will be exciting to see the advancement over the next 5–10 years.

Acknowledgments

Sara L. Appleton-Knapp reports salary from a grant from NIH - R01 DK103554 02S1, during the writing of this paper.

Kerri N. Boutelle reports grants from NIH (R01DK094475; R01DK103554; K02HL112042).

References

1. Hudson JI, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatr*. 2007; 61:348–58.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the united states, 2011–2012. *JAMA*. 2014; 311(8):806–14. [PubMed: 24570244]
3. Fairburn CG, Bailey-Straebl S, Basden S, Doll HA, Jones R, Murphy R, et al. A transdiagnostic comparison of enhanced cognitive behaviour therapy (CBT-E) and interpersonal psychotherapy in the treatment of eating disorders. *Behav Res Ther*. 2015; 70:64–71. [PubMed: 26000757]
4. Wadden TA, West DS, Neiberg R, Wing RR, Ryan DH, Johnson KC, et al. One-Year Weight Losses in the Look AHEAD Study: Factors Associated with Success. *Obes*. 2009; 17(4):713–22.
5. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, et al. Four-Year Weight Losses in the Look AHEAD Study: Factors Associated with Long-Term Success. *Obes*. 2011; 19(10):1987–98.
6. Bulik CM. The challenges of treating anorexia nervosa. *Lancet*. 2014; 383(9912):105–6. [PubMed: 24131860]
7. Moroshko I, Brennan L, O'Brien P. Predictors of dropout in weight loss interventions: a systematic review of the literature. *Obes Rev*. 2011; 12(11):912–34. [PubMed: 21815990]
8. Fitzpatrick S, Gilbert S, Serpell L. Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? *Neuropsychol Rev*. 2013; 23(2):138–56. [PubMed: 23381140]
9. Fagundo AB, De la Torre R, Jiménez-Murcia S, Agüera Z, Granero R, Tárrega S, et al. Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. *PloS one*. 2012; 7(8):e43382. [PubMed: 22927962]
10. Diamond A. Executive functions. *Annual review of psychology*. 2013; 64:135–68.
11. Chen J, Papies EK, Barsalou LW. A core eating network and its modulations underlie diverse eating phenomena. *Brain and Cogn*. 2016; 110:20–42. Authors propose a neural network that underlies eating behaviors, providing a framework for understanding neural deficits and how they contribute to disordered eating.
12. Aloï M, Rania M, Caroleo M, Bruni A, Palmieri A, Cauteruccio MA, et al. Decision making, central coherence and set-shifting: a comparison between Binge Eating Disorder, Anorexia Nervosa and Healthy Controls. *BMC Psychiatr*. 2015; 15(1):6.
13. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends in Neurosci*. 2013; 36(2):110–20.
14. Reville M-C, O'Connor L, Frampton I. Literature review of cognitive neuroscience and anorexia nervosa. *Curr Psychiatr Rep*. 2016; 18(2):1–8.
15. Decker JH, Figner B, Steinglass JE. On Weight and Waiting: Delay Discounting in Anorexia Nervosa Pretreatment and Posttreatment. *Biol Psychiatr*. 2015; 78(9):606–14.
16. Steinglass J, Figner B, Berkowitz S, Simpson HB, Weber EU, Walsh BT. Increased Capacity to Delay Reward in Anorexia Nervosa. *Journal of the International Neuropsychological Society : JINS*. 2012; 18(4):773–80. [PubMed: 22591835]

17. Wierenga CE, Bischoff-Grethe A, Melrose AJ, Irvine Z, Torres L, Bailer UF, et al. Hunger does not motivate reward in women remitted from anorexia nervosa. *Biol Psychiatry*. 2015; 77(7):642–52.
18. Roberts ME, Tchanturia K, Treasure JL. Overlapping neurocognitive inefficiencies in anorexia nervosa: a preliminary investigation of women with both poor set-shifting and weak central coherence. *Eat and Weight Disord*. 2016; 21(4):725–9.
19. Lang K, Lopez C, Stahl D, Tchanturia K, Treasure J. Central coherence in eating disorders: An updated systematic review and meta-analysis. *World J of Biol Psychiatry*. 2014; 15(8):586–98. [PubMed: 24882144]
20. Wu M, Hartmann M, Skunde M, Herzog W, Friederich H-C. Inhibitory Control in Bulimic-Type Eating Disorders: A Systematic Review and Meta-Analysis. *PloS one*. 2014; 8(12):e83412.
21. Kekic M, Bartholdy S, Cheng J, McClelland J, Boysen E, Musiat P, et al. Increased temporal discounting in bulimia nervosa. *Int J Eat Disord*. 2016; 49(12):1077–81. [PubMed: 27301653]
22. Weider S, Indredavik MS, Lydersen S, Hestad K. Neuropsychological function in patients with anorexia nervosa or bulimia nervosa. *Int J Eat Disord*. 2015; 48(4):397–405. [PubMed: 24719259]
23. Degortes D, Tenconi E, Santonastaso P, Favaro A. Executive functioning and visuospatial abilities in bulimia nervosa with or without a previous history of anorexia nervosa. *Eur Eat Disord Rev*. 2016; 24(2):139–46. [PubMed: 26708940]
24. Seitz J, Hueck M, Dahmen B, Schulte-Rüther M, Legenbauer T, Herpertz-Dahlmann B, et al. Attention Network Dysfunction in Bulimia Nervosa-An fMRI Study. *PloS one*. 2016; 11(9):e0161329. [PubMed: 27607439]
25. Wierenga CE, Ely A, Bischoff-Grethe A, Bailer UF, Simmons AN, Kaye WH. Are extremes of consumption in eating disorders related to an altered balance between reward and inhibition? *Front in Behav Neurosci*. 2014; 8:410.
26. Manasse SM, Juarascio AS, Forman EM, Berner LA, Butryn ML, Ruocco AC. Executive Functioning in Overweight Individuals with and without Loss-of-Control Eating. *Eur Eat Disord Rev*. 2014; 22(5):373–7. [PubMed: 24962637]
- 27••. Lavagnino L, Arnone D, Cao B, Soares JC, Selvaraj S. Inhibitory control in obesity and binge eating disorder: A systematic review and meta-analysis of neurocognitive and neuroimaging studies. *Neurosci & Biobehav Rev*. 2016; 68:714–26. This systematic review summarizes the existing literature on inhibitory control and obesity/BED, indicating that obese children and adults have inhibitory control deficits compared to healthy weight counterparts. Further, this study conducted a meta-analysis on studies using the stop-signal task in overweight/obese populations compared to healthy weight controls as well as obese populations with BED compared to obese populations without BED, finding inhibitory control deficits for overweight/obese populations but no differences based on BED status. [PubMed: 27381956]
28. Kessler RM, Hutson PH, Herman BK, Potenza MN. The neurobiological basis of binge-eating disorder. *Neurosci & Biobehav Rev*. 2016; 63:223–38. [PubMed: 26850211]
29. Geliebter A, Benson L, Pantazatos SP, Hirsch J, Carnell S. Greater anterior cingulate activation and connectivity in response to visual and auditory high-calorie food cues in binge eating: preliminary findings. *Appetite*. 2016; 96:195–202. [PubMed: 26275334]
- 30••. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev*. 2011; 12(9):740–55. This is a review on the literature investigating the relationship between obesity and neurocognitive functioning across the lifespan, from children to the elderly. This review highlights the association between executive function and weight gain, and suggests important mechanisms that may be at play in this bidirectional relationship. [PubMed: 21991597]
- 31••. Liang J, Matheson BE, Kaye WH, Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. *Int J Obes*. 2014; 38(4):494–506. This review summarizes the literature examining neurocognitive functioning and overweight/obesity and obesity-related behaviors in children and youth. This review found evidence that suggests a negative relationship between obesity and executive functioning, attention, visuo-spatial performance, and motor skills with less support for a clear link between obesity and general cognitive functioning, language, learning and memory, and academic achievement.

32. Schiff S, Amodio P, Testa G, Nardi M, Montagnese S, Caregaro L, et al. Impulsivity toward food reward is related to BMI: evidence from intertemporal choice in obese and normal-weight individuals. *Brain and Cogn.* 2016; 110:112–9.
33. Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: a systematic literature review. *Obes Res & Clin Prac.* 2015; 9(2):93–113.
34. Sargénus HL, Lydersen S, Hestad K. Neuropsychological function in individuals with morbid obesity: a cross-sectional study. *BMC Obes.* 2017; 4(1):6. [PubMed: 28138392]
35. Tchanturia K, Davies H, Roberts M, Harrison A, Nakazato M, Schmidt U, et al. Poor cognitive flexibility in eating disorders: examining the evidence using the Wisconsin Card Sorting Task. *PloS one.* 2012; 7(1):e28331. [PubMed: 22253689]
36. Juarascio AS, Manasse SM, Espel HM, Kerrigan SG, Forman EM. Could training executive function improve treatment outcomes for eating disorders? *Appetite.* 2015; 90:187–93. [PubMed: 25777264]
- 37••. Tchanturia K, Lloyd S, Lang K. Cognitive remediation therapy for anorexia nervosa: current evidence and future research directions. *Int J Eat Disord.* 2013; 46(5):492–5. This paper provides an overview of CRT for AN, reviews published and unpublished study findings, and suggests future directions for the utility of CRT in ED treatment. [PubMed: 23658098]
- 38•••. Stice E, Lawrence NS, Kemps E, Veling H. Training motor responses to food: A novel treatment for obesity targeting implicit processes. *Clin Psychol Rev.* 2016; 49:16–27. This article reviews the evidence behind targeting Inhibition in Obesity Treatment. [PubMed: 27498406]
39. Roberts ME, Tchanturia K, Stahl D, Southgate L, Treasure J. A systematic review and meta-analysis of set-shifting ability in eating disorders. *Psychol Med.* 2007; 37(8):1075–84. [PubMed: 17261218]
40. Brockmeyer T, Ingernerf K, Walther S, Wild B, Hartmann M, Herzog W, et al. Training cognitive flexibility in patients with anorexia nervosa: a pilot randomized controlled trial of cognitive remediation therapy. *Int J of Eat Disord.* 2014; 47(1):24–31. [PubMed: 24166941]
41. Brockmeyer T, Walther S, Ingernerf K, Wild B, Hartmann M, Weisbrod M, et al. Brain effects of computer-assisted cognitive remediation therapy in anorexia nervosa: A pilot fMRI study. *Psychiatry Res.* 2016; 249:52–6. [PubMed: 27000307]
42. Genders R, Tchanturia K. Cognitive remediation therapy (CRT) for anorexia in group format: a pilot study. *Eat and Weight Disord.* 2010; 15(4):e234–9.
43. Tchanturia K, Lounes N, Holtum S. Cognitive remediation in anorexia nervosa and related conditions: a systematic review. *Eur Eat Disord Rev.* 2014; 22(6):454–62. [PubMed: 25277720]
44. Zuchova S, Erler T, Papezova H. Group cognitive remediation therapy for adult anorexia nervosa inpatients: first experiences. *Eat and Weight Disord.* 2013; 18(3):269–73.
45. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *The Am J of Psychiatry.* 2011; 168(5):472–85. [PubMed: 21406461]
46. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiat.* 2007; 164(12):1791–802. [PubMed: 18056233]
47. Elgamal S, McKinnon MC, Ramakrishnan K, Joffe RT, MacQueen G. Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. *Psychol Med.* 2007; 37(9):1229–38. [PubMed: 17610766]
48. Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch of Phys Med and Rehabil.* 2005; 86(8):1681–92. [PubMed: 16084827]
49. Danner UN, Dingemans AE, Steinglass J. Cognitive remediation therapy for eating disorders. *Curr Opin in Psychiatry.* 2015; 28(6):468–72.
- 50•••. Dahlgren CL, Ro O. A systematic review of cognitive remediation therapy for anorexia nervosa - development, current state and implications for future research and clinical practice. *J of Eat Disord.* 2014; 2(1):26. This systematic review investigates the use of CRT for the treatment of AN. In particular, this review highlights four RCT's with initial promising results in terms of reduction in both attrition and eating disorder symptoms as well as increased set-shifting and quality of life. [PubMed: 25254110]

51. Lock J, Agras WS, Fitzpatrick KK, Bryson SW, Jo B, Tchanturia K. Is outpatient cognitive remediation therapy feasible to use in randomized clinical trials for anorexia nervosa? *Int J of Eat Disord.* 2013; 46(6):567–75. [PubMed: 23625628]
52. Steinglass JE, Albano AM, Simpson HB, Wang YJ, Zou JJ, Attia E, et al. Confronting Fear Using Exposure and Response Prevention for Anorexia Nervosa: A Randomized Controlled Pilot Study. *Int J of Eat Disord.* 2014; 47(2):174–80. [PubMed: 24488838]
53. Dingemans AE, Danner UN, Donker JM, Aardoom JJ, van Meer F, Tobias K, et al. The effectiveness of cognitive remediation therapy in patients with a severe or enduring eating disorder: a randomized controlled trial. *Psychother and Psychosom.* 2014; 83(1):29–36.
54. Giombini L, Moynihan J, Turco M, Nesbitt S. Evaluation of individual cognitive remediation therapy (CRT) for the treatment of young people with anorexia nervosa. *Eat and Weight Disord.* 2016
55. van Noort BM, Kraus MK, Pfeiffer E, Lehmkuhl U, Kappel V. Neuropsychological and Behavioural Short-Term Effects of Cognitive Remediation Therapy in Adolescent Anorexia Nervosa: A Pilot Study. *Eur Eat Disord Rev.* 2016; 24(1):69–74. [PubMed: 26189926]
56. Wood L, Al-Khairulla H, Lask B. Group cognitive remediation therapy for adolescents with anorexia nervosa. *Clin Child Psychol and Psychiatry.* 2011; 16(2):225–31.
57. Pretorius N, Dimmer M, Power E, Eisler I, Simic M, Tchanturia K. Evaluation of a cognitive remediation therapy group for adolescents with anorexia nervosa: pilot study. *Eur Eat Disord Rev.* 2012; 20(4):321–5. [PubMed: 22488792]
58. Lang K, Stahl D, Espie J, Treasure J, Tchanturia K. Set shifting in children and adolescents with anorexia nervosa: an exploratory systematic review and meta-analysis. *Int J of Eat Disord.* 2014; 47(4):394–9. [PubMed: 24347025]
59. Fagundo AB, Santamaria JJ, Forcano L, Giner-Bartolome C, Jimenez-Murcia S, Sanchez I, et al. Video game therapy for emotional regulation and impulsivity control in a series of treated cases with bulimia nervosa. *Eur Eat Disord Rev.* 2013; 21(6):493–9. [PubMed: 24092598]
60. Giner-Bartolome C, Fagundo AB, Sanchez I, Jimenez-Murcia S, Santamaria JJ, Ladouceur R, et al. Can an intervention based on a serious videogame prior to cognitive behavioral therapy be helpful in bulimia nervosa? A clinical case study. *Front in Psychol.* 2015; 6
61. Hofmann W, Friese M, Roefs A. Three ways to resist temptation: The independent contributions of executive attention, inhibitory control, and affect regulation to the impulse control of eating behavior. *J Exp Soc Psychol.* 2009; 45(2):431–5.
62. Appelhans BM. Neurobehavioral inhibition of reward-driven feeding: implications for dieting and obesity. *Obes.* 2009; 17(4):640–7.
63. Bar-Haim Y. Research review: Attention bias modification (ABM): a novel treatment for anxiety disorders. *J Child Psychol and Psychiatry, and allied disciplines.* 2010; 51(8):859–70.
64. Renwick B, Campbell IC, Schmidt U. Review of attentional bias modification: a brain-directed treatment for eating disorders. *Eur Eat Disord Rev.* 2013; 21(6):464–74. [PubMed: 24002738]
65. Boutelle KN, Monreal T, Strong DR, Amir N. An open trial evaluating an attention bias modification program for overweight adults who binge eat. *J Behav Ther and Exp Psychiatry.* 2016; 52:138–46. [PubMed: 27116704]
66. Giel KE, Schag K, Plewnia C, Zipfel S. Antisaccadic Training to Improve Impulsivity in Binge Eating Disorder. *Eur Eat Disord Rev.* 2013; 21(6):488–92. [PubMed: 23893405]
67. Schag K, Teufel M, Junne F, Preissl H, Hautzinger M, Zipfel S, et al. Impulsivity in binge eating disorder: food cues elicit increased reward responses and disinhibition. *PloS one.* 2013; 8(10):e76542. [PubMed: 24146885]
68. Giel KE, Speer E, Schag K, Leehr EJ, Zipfel S. Effects of a food-specific inhibition training in individuals with binge eating disorder—findings from a randomized controlled proof-of-concept study. *Eat and Weight Disord.* 2017:1–7.
69. Schag K, Leehr EJ, Martus P, Bethge W, Becker S, Zipfel S, et al. Impulsivity-focused group intervention to reduce binge eating episodes in patients with binge eating disorder: study protocol of the randomised controlled IMPULS trial. *BMJ open.* 2015; 5(12):e009445.
- 70•••. Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: A

systematic review and meta-analysis. *Neurosci & Biobehav Rev.* 2017; 72:87–94. The results of this meta-analysis indicated a relationship between weight loss and improvements in neurocognitive functioning, primarily in the areas of attention, memory, executive function and language. [PubMed: 27890688]

71. Naar-King S, Ellis DA, Carcone AI, Templin T, Jacques-Tiura AJ, Hartlieb KB, et al. Sequential Multiple Assignment Randomized Trial (SMART) to Construct Weight Loss Interventions for African American Adolescents. *J Clin Child Adolesc.* 2016; 45(4):428–41.
72. Wing RR, Tate DF, Espeland MA, Lewis CE, LaRose JG, Gorin AA, et al. Innovative Self-Regulation Strategies to Reduce Weight Gain in Young Adults The Study of Novel Approaches to Weight Gain Prevention (SNAP) Randomized Clinical Trial. *JAMA Intern Med.* 2016; 176(6): 755–62. [PubMed: 27136493]
73. Warschburger P. SRT-Joy - computer-assisted self-regulation training for obese children and adolescents: study protocol for a randomized controlled trial. *Trials.* 2015; 16
74. Raman J, Hay P, Smith E. Manualised Cognitive Remediation Therapy for adult obesity: study protocol for a randomised controlled trial. *Trials.* 2014; 15:426. [PubMed: 25370364]
75. Smith E, Whittingham C. Cognitive remediation therapy plus behavioural weight loss compared to behavioural weight loss alone for obesity: study protocol for a randomised controlled trial. *Trials.* 2017; 18(1):42. [PubMed: 28126015]
- 76••. Miller AL. Neurocognitive Processes and Pediatric Obesity Interventions: Review of Current Literature and Suggested Future Directions. *Pediatr Clin N Am.* 2016; 63(3):447–57. This review not only highlights the important relationship between self-regulation and executive functioning and obesity in children, it also discusses potential pathways that connect executive function deficits with weight gain in children.
77. Bustamante EE, Williams CF, Davis CL. Physical Activity Interventions for Neurocognitive and Academic Performance in Overweight and Obese Youth: A Systematic Review. *Pediatr Clin N Am.* 2016; 63(3):459–80.
78. Staiano AE, Abraham AA, Calvert SL. Competitive versus cooperative exergame play for African American adolescents' executive function skills: short-term effects in a long-term training intervention. *Dev Psychol.* 2012; 48(2):337–42. [PubMed: 22369339]
79. Veling H, Lawrence NS, Chen Z, van Koningsbruggen GM, Holland RW. What Is Trained During Food Go/No-Go Training? A Review Focusing on Mechanisms and a Research Agenda. *Curr Addict Rep.* 2017;1–7. [PubMed: 28357191]
80. Verbeken S, Braet C, Goossens L, van der Oord S. Executive function training with game elements for obese children: A novel treatment to enhance self-regulatory abilities for weight-control. *Behav Res Ther.* 2013; 51(6):290–9. [PubMed: 23524063]
81. Lawrence NS, O'Sullivan J, Parslow D, Javaid M, Adams RC, Chambers CD, et al. Training response inhibition to food is associated with weight loss and reduced energy intake. *Appetite.* 2015; 95:17–28. [PubMed: 26122756]
82. Veling H, van Koningsbruggen GM, Aarts H, Stroebe W. Targeting impulsive processes of eating behavior via the internet. Effects on body weight *Appetite.* 2014; 78:102–9. [PubMed: 24675683]
83. Kemps E, Tiggemann M, Orr J, Grear J. Attentional Retraining Can Reduce Chocolate Consumption. *J Exp Psychol-Appl.* 2014; 20(1):94–102. [PubMed: 24079387]
84. Kemps E, Tiggemann M, Elford J. Sustained effects of attentional re-training on chocolate consumption. *J of Behav Ther and Exp Psychiatry.* 2015; 49(Pt A):94–100. [PubMed: 25537425]
85. Adams RC, Lawrence NS, Verbruggen F, Chambers CD. Training response inhibition to reduce food consumption: Mechanisms, stimulus specificity and appropriate training protocols. *Appetite.* 2017; 109:11–23. [PubMed: 27838443]
86. Jones A, Di Lemma LCG, Robinson E, Christiansen P, Nolan S, Tudur-Smith C, et al. Inhibitory control training for appetitive behaviour change: A meta-analytic investigation of mechanisms of action and moderators of effectiveness. *Appetite.* 2016; 97:16–28. [PubMed: 26592707]
87. Boutelle KN, Bouton ME. Implications of learning theory for developing programs to decrease overeating. *Appetite.* 2015; 93:62–74. [PubMed: 25998235]
88. Boutelle KN, Liang J, Knatz S, Matheson B, Risbrough V, Strong D, et al. Design and implementation of a study evaluating extinction processes to food cues in obese children: the

Intervention for Regulations of Cues Trial (iROC). *Contemp Clin Trials*. 2015; 40:95–104. [PubMed: 25461494]

89. Jansen A, Schyns G, Bongers P, van den Akker K. From lab to clinic: Extinction of cued cravings to reduce overeating. *Physiol & Behav*. 2016; 162:174–80. [PubMed: 26994737]
90. Petanjek Z, Judaš M, Šimić G, Rašin MR, Uylings HBM, Rakic P, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc of the Natl Acad of Sciences*. 2011; 108(32): 13281–6.