

Citicoline Affects Appetite and Cortico-Limbic Responses to Images of High-Calorie Foods

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ABSTRACT

Objective: Cytidine-5'-diphosphocholine (citicoline) has a variety of cognitive enhancing, neuroprotective, and neuroregenerative properties. In cocaine-addicted individuals, citicoline has been shown to increase brain dopamine levels and reduce cravings. The effects of this compound on appetite, food cravings, and brain responses to food are unknown.

Method: We compared the effects of treatment with Cognizin[®] citicoline (500 mg/day versus 2,000 mg/day) for 6 weeks on changes in appetite ratings, weight, and cortico-limbic responses to images of high-calorie foods using functional magnetic resonance imaging (fMRI).

Results: After 6 weeks, there was no significant change in weight status, although

significant declines in appetite ratings were observed for the 2,000 mg/day group. The higher dose group also showed significant increases in functional brain responses to food stimuli within the amygdala, insula, and lateral orbitofrontal cortex. Increased activation in these regions correlated with declines in appetite ratings.

Discussion: These preliminary findings suggest a potential usefulness of citicoline in modulating appetite, but further research is warranted. © 2009 by Wiley Periodicals, Inc.

Keywords: citicoline; cytidine-5'-diphosphocholine; fMRI; neuroimaging; food; appetite; orbitofrontal cortex; insula; amygdala

(*Int J Eat Disord* 2010; 43:6–13)

Introduction

The epidemic of obesity is one of the most pressing health concerns of the 21st century.¹ The factors that lead to poor appetite control, excessive weight gain, and obesity are multifaceted, but neuroscience research is making headway into clarifying the neuro-cognitive systems involved in regulating appetite and food intake. Hormones such as insulin, leptin, and ghrelin on the homeostatic func-

tions of the hypothalamus have long been known to mediate appetitive responses, but recent evidence suggests that these hormones may also have direct effects on dopamine neurons, which in turn may have a more immediate and direct effect on the motivation to eat and the reward value of food.^{2,3} Because of its primary involvement in reward and motivation, the dopamine system is implicated in a variety of substance abuse/addictive behavior disorders such as cocaine addiction and pathological gambling.^{4,5} The involvement of the dopamine system in appetite and eating behavior suggests that dopaminergic-reward models of craving and substance-dependence may potentially apply to the regulation of food intake.^{6–8}

In cocaine addicted individuals, preliminary evidence suggests that it may be possible to reduce drug cravings through the administration of cytidine-5'-diphosphocholine (citicoline).⁹ Furthermore, one recent randomized, placebo-controlled study found that cocaine dependent outpatients treated with citicoline were less likely to screen positive for cocaine by the end of the trial.¹⁰ Citicoline, which is marketed as a nutritional supplement and widely available in health food stores, is essentially a complex organic molecule that has

Accepted 20 December 2008

P.F.R. and D.Y.T. serve as consultants to and T.K. and Y.K. are employees of Kyowa Hakko Kogyo Co., Ltd., Japan.

Supported by 1R01 DA020269 from NIDA and by Kyowa Hakko Kogyo Co., Ltd., Japan.

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Published online 3 March 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/eat.20658

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been shown to have a variety of cognitive enhancing, neuroprotective, and neuroregenerative properties,^{11–13} although findings are far from conclusive.^{14,15} Some evidence suggests that citicoline may affect the dopamine system,¹³ thereby altering the reward value of stimuli. As a nucleotide molecule, citicoline is involved in cellular metabolism and biosynthesis of phospholipids.¹⁶ When taken orally, exogenous citicoline undergoes hydrolysis in the small intestine, where it is absorbed as choline and cytidine.¹⁷ Because it is water-soluble, citicoline is rapidly hydrolyzed and absorbed into the blood stream, demonstrating over 90% bioavailability.^{16,18} Once absorbed, choline and cytidine are circulated throughout the body and become available to a variety of biosynthetic systems, and readily cross the blood-brain barrier where they are synthesized once again into citicoline.¹⁹ It has been suggested that exogenous administration of citicoline can help preserve endogenous choline reserves and minimize cell membrane phospholipid catabolism, a process that may occur when the demand for acetylcholine exceeds available stores of endogenous choline.^{17,18} Citicoline is believed exert a variety of effects on the central nervous system via synthesis of acetylcholine and phosphatidylcholine,¹⁸ restoration of membrane phospholipid components such as cardiolipin²⁰ and sphingomyelin,²¹ and enhancement of neurotransmitters such as norepinephrine and dopamine.^{22–25} A number of studies have suggested that citicoline administration has several effects on the dopamine system, including increasing the levels of dopamine in neural tissues,^{23,26} increasing dopamine receptor densities,²⁷ and neuroprotection of dopamine neurons.²⁸ The effects of citicoline on the dopamine-reward system in conjunction with preliminary evidence of its effectiveness at reducing cravings in cocaine users⁹ raises the possibility that citicoline may also have the potential to affect appetite and food cravings.

Citicoline has been studied extensively in recent years for a variety of cognitive enhancing and neuroprotective functions, but there have been no investigations into the potential effects of this compound on appetite and cerebral responses to food. Therefore, we conducted a preliminary evaluation of two different doses of citicoline (500 mg/day vs. 2,000 mg/day) administered daily for 6 weeks on changes in appetite and cortico-limbic responses to images of high-calorie foods during functional magnetic resonance imaging (fMRI). It was hypothesized that the higher of the two doses of citicoline would be associated with greater declines

in appetite ratings and increased activation within brain regions that are involved in inhibitory control, satiation, and withdrawal responses relative to the lower dose, and that these changes in brain activation would predict appetite changes. We focused our analyses on three regions based on previous research suggesting that they are particularly important in appetite. First, we focused on the lateral orbitofrontal cortex, a region that functions as part of the gustatory cortex and is often activated in studies using appetizing food images.^{29,30} Furthermore, the lateral orbitofrontal cortex (OFC) is involved in behavioral control and has been shown to be more active when an individual feels sated³¹ and when stimuli are perceived as less rewarding.³² Therefore, this region was selected for specific study. Second, we focused on the insular cortex, as evidence suggests that it is involved in visceral bodily sensations such as those that occur during disgust responses^{33,34} and interoceptive awareness of somatic states,³⁵ and is commonly activated in studies showing photographs of appetizing foods.^{30,36,37} Finally, because the amygdala is often involved in responses to food stimuli and appetite,^{38,39} particularly in obese individuals,⁴⁰ we also hypothesized that this region would be affected by administration of citicoline.

Method

Participants

Sixteen healthy adults (8 men; 8 women; 12 right-handed by self-report) ranging from 40 to 57 years ($M = 47.3$, $SD = 5.4$) were recruited from the community of Belmont, MA. At intake, the body mass index (BMI) of participants ranged from 20.1 to 38.6 ($M = 25.3$, $SD = 5.2$). Volunteers were screened for a wide range of potential medical, psychiatric, and health concerns and only those participants that were deemed to be in good medical and psychiatric health were included. Participants had normal or corrected-normal vision (with contact lenses). The present study was conducted under the guidelines of the McLean Hospital Institutional Review Board. All participants provided written informed consent and were given a small financial compensation for their participation.

Study Design

Participants completed two interview/functional imaging scanning sessions separated by 6 weeks. At the first visit, participants completed a medical and psychiatric interview and several questionnaires about food and lifestyle preferences, and were asked to rate their typical appetite on a 10-point Likert scale from 1 (never hungry)

to 10 (always hungry). Following the interview and questionnaires, participants underwent an fMRI scan to examine responses to images of high-calorie foods. Participants were scanned at approximately the same time of day to minimize circadian influences. No attempts were made to restrict food intake before the scans and participants were allowed to follow their normal diets. In an open label design, participants were randomly assigned to one of two conditions, a low dose or a high dose administration of citicoline (Cognizin[®], Kyowa Hakko Kogyo, Japan). Eight participants (four male, four female) were assigned to consume the low dose (i.e., one 500 mg capsule/day) of citicoline over the intervening 6-week period, whereas the other eight participants were assigned to consume the high dose (i.e., four 500 mg capsules/day) during the same time period. Participants were contacted by telephone twice per week to improve compliance and to allow for reporting of any adverse effects. Participants returned to the neuroimaging center to repeat the questionnaires and fMRI scanning procedure after 6 weeks of treatment. Changes in appetite ratings and weight were calculated for each participant by subtracting scores at Visit 1 from those at Visit 2.

Imaging Methods

Functional images were acquired on a Siemens Trio whole body 3T MRI scanner equipped with a quadrature RF head coil (TR = 3 sec, TE = 30 ms, flip angle = 90 degrees). Fifty images per slice were collected over 35 to 41 coronal slices (5 mm thick, 0 skip) with a 20 cm field of view and a 64 × 64 acquisition matrix (in-plane resolution = 3.125 × 5 × 3.125 mm³) using a single-shot, gradient pulse-echo sequence. To allow the scanner to reach a steady-state, three dummy images were acquired at the start of each functional scan and discarded from analysis. The participant's head was secured using foam padding.

Stimulation Paradigms

The stimulation paradigm has been described in detail in several previous reports.^{38,41–43} In brief, participants were scanned while viewing a series of colorful visual images that included both high-calorie foods (e.g., cheeseburgers, hot dogs, french-fries, ice cream, cake, cookies) and control images of non-food objects with similar visual complexity, texture, and color (e.g., rocks, shrubs, bricks, trees, flowers). The stimulation paradigm was 150 sec in duration, and comprised five alternating 30-sec periods (i.e., control, high-calorie, control, high-calorie, control). Each alternating block consisted of 10 photographs (2,500 ms stimulus presentation and a 500 ms inter-stimulus interval). Stimuli were controlled by a Macintosh computer running Psyscope⁴⁴ and were back-projected onto a screen placed at the rear of the scanner. Participants viewed the stimuli via a mirror mounted on

the head coil. The same stimuli were presented at baseline and again following 6 weeks of treatment.

Image Processing and Analysis

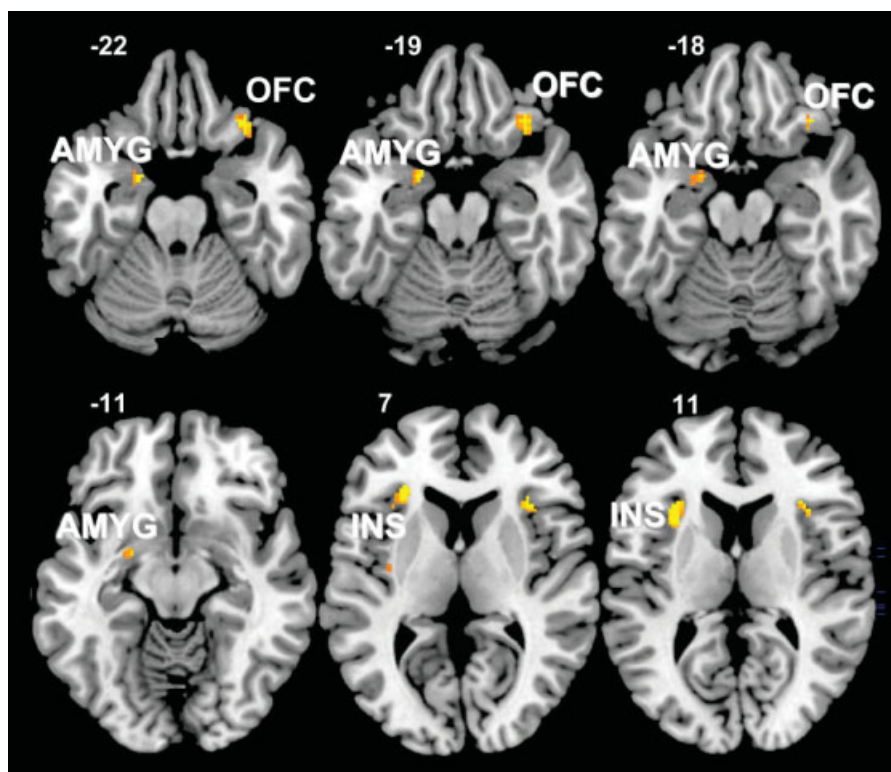
Data were preprocessed and analyzed in SPM99.⁴⁵ Images were motion corrected, convolved into the standard Montreal Neurological Institute (MNI) space, smoothed using an isotropic Gaussian kernel (full width half maximum = 6 mm), and resliced to 2 × 2 × 2 mm³ voxels using sinc interpolation. Data analysis was completed in two stages. At the first stage, contrast images were constructed to evaluate activation specific to viewing the high-calorie food images relative to the nonfood control images. Within-subject contrast images were also created to determine regions of change between Visit 1 and Visit 2. In the second, or “random-effects” level of analysis, these change images were entered into a between groups *t*-test to compare the effects of low- versus high-dose citicoline. The change images were also entered into a simple linear regression model in SPM99 with appetite change scores entered as the covariate of interest. Three region of interest (ROI) masks were created using the WFU Pickatlas utility⁴⁶ to restrict analyses to only pre-specified areas. On the basis of previous research showing that food images are associated with activation of the amygdala,^{37,38,40,42} insula,^{30,37,40} and lateral OFC,^{30,40,43} these three regions were analyzed using the published anatomical atlas of Tzourio-Mazoyer et al.⁴⁷ Because these three ROIs were predicted a priori to be affected by citicoline and to show functional changes with appetite ratings, we used a statistical threshold of $p < .05$, $k = 10$ contiguous voxels. Exploratory whole brain analyses were undertaken at a more stringent threshold of $p < .001$, $k = 10$ for the direct contrasts between baseline and post-treatment and the correlation analyses.

Results

Appetite Ratings and Weight

Self-rated appetite declined significantly between Visit 1 ($M = 6.8$, $SD = 1.5$) and Visit 2 ($M = 6.1$, $SD = 1.5$) for the sample as a whole, $t(15) = -2.83$, $p = .02$. The mean change scores for both groups declined between visits, but the magnitude of decline only reached significance for the high-dose group ($M = -0.88$, $SD = 0.83$), $t(7) = -2.97$, $p = .02$, while the decline for the low-dose group did not ($M = -0.38$, $SD = 0.92$), $t(7) = -1.16$, $p = .29$. Between group comparison of these changes did not reach statistical significance, however, $t(14) = 1.14$, $p = .27$. Similarly, there was no significant change in weight from Visit 1 to Visit 2 for the low ($M = -6.4$

FIGURE 1. Axial slices showing significantly greater increases in functional activation after 6 weeks of treatment with high-dose citicoline (2,000 mg/day) versus the low-dose (500 mg/day) treatment during the food perception task. Activation is shown only within the three regions of interest, including the left amygdala (AMYG), bilateral insula (INS), and right lateral orbitofrontal cortex (OFC).



lbs, $SD = 11.0$, $t(6) = -1.55$, $p = .17$) or high ($M = -0.57$ lbs, $SD = 3.8$, $t(6) = -0.40$, $p = .71$) dose groups and the magnitude of weight change did not differ between the two groups, $t(13) = 1.55$, $p = .15$.

Dose Group Comparisons

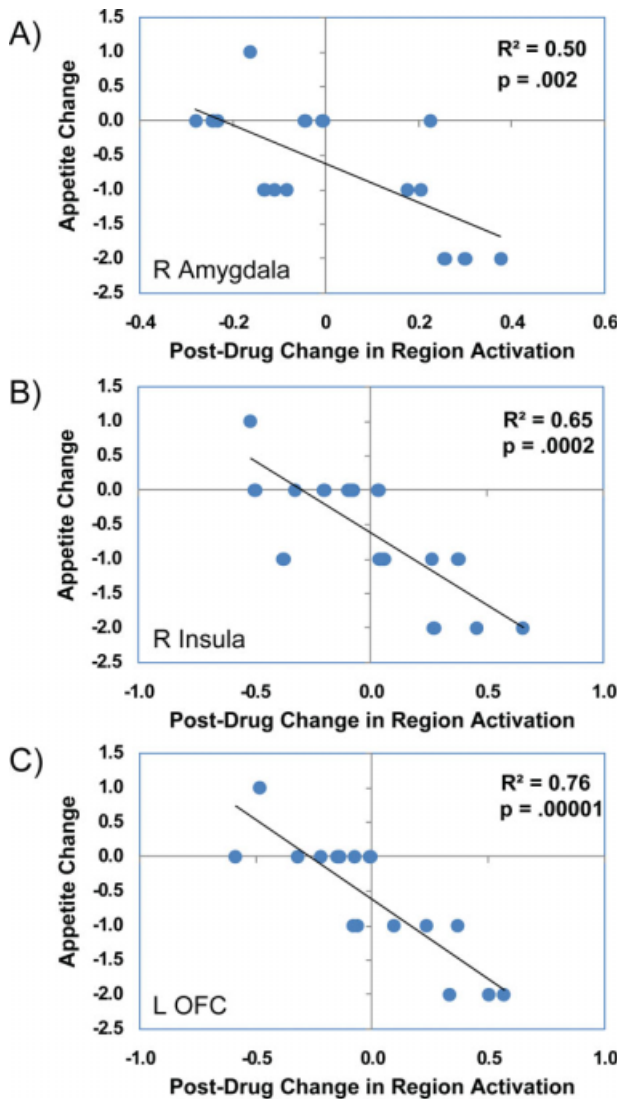
The effects of high- versus low-dose citicoline on changes in brain activation were compared for the three ROIs. As evident in **Figure 1**, the high-dose group showed significantly greater between-visit increases in activation within the left amygdala ($T = 2.25$, 40 voxels, MNI coordinates: $x = -20$, $y = 0$, $z = -22$), bilateral insula ($T = 3.59$, 92 voxels, MNI coordinates: $x = -28$, $y = 32$, $z = 6$; $T = 3.49$, 25 voxels; MNI coordinates: $x = 34$, $y = 22$, $z = 10$; $T = 1.99$, 10 voxels, MNI coordinates: $x = -36$, $y = -10$, $z = 6$), and right lateral OFC ($T = 2.76$, 41 voxels, MNI coordinates: $x = 34$, $y = 30$, $z = -22$) relative to the low-dose group. In contrast, there were no ROIs where low-dose citicoline produced greater change than high-dose citicoline. In contrast to the ROIs, exploratory whole brain comparisons revealed that only one region, located within the right cerebellum ($T = 4.35$, 10 voxels, MNI coordinates: $x =$

30 , $y = -56$, $z = -24$), showed significantly greater change in activation in the high-dose group relative to the low-dose group. In contrast, there were no regions that showed greater pre-post changes in activation in the low-dose group relative to the high-dose group for the exploratory whole brain analysis.

Correlation Between Brain Activation and Appetite Changes

Changes in regional brain activation from Visit 1 to Visit 2 were used to predict corresponding changes in appetite ratings. As evident in **Figure 2**, changes in ROI activation when viewing high-calorie food images were associated with changes in appetite between the two visits. Specifically, participants that showed the greatest increase in the task-related activation of the right amygdala ($T = 3.76$, 146 voxels, $x = 28$, $y = -2$, $z = -24$), bilateral insula ($T = 5.09$, 865 voxels, $x = 36$, $y = 12$, $z = 4$; $T = 4.36$, 22 voxels, $x = -28$, $y = 22$, $z = -20$; $T = 3.75$, 624 voxels, $x = -42$, $y = 10$, $z = -6$), and left lateral OFC ($T = 6.63$, 532 voxels, $x = -36$, $y = 22$, $z = -16$; $T = 4.22$, 549 voxels, $x = 26$, $y = 24$, $z = -14$) tended to show the greatest declines in appe-

FIGURE 2. The scatter plots show the correlations between changes in brain activation in response to the food perception task and changes in appetite ratings following 6 weeks of treatment with citicoline in the maximally correlated voxel for (A) the right amygdala, (B) right insula, and (C) left lateral orbitofrontal cortex (see text for MNI coordinates). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



tite ratings between the two visits. The correlations were similar for the low-dose (i.e., right amygdala $r = -.63, p = .085$; right insula $r = -.89, p = .003$; left OFC $r = -.91, p = .002$) and high-dose (i.e., right amygdala $r = -.91, p = .002$; right insula $r = -.70, p = .051$; left OFC $r = -.88, p = .004$) groups. Exploratory analysis of the correlations at the whole brain level revealed no regions showing positive correlations between changes in brain activation and changes in appetite ratings, but did show a number of negatively correlated clusters where

TABLE 1. Whole brain analysis showing regions where increased brain activation from pre–post citicoline administration was correlated with significant declines in appetite ratings

| Region | Number of Voxels | x | y | z | SPM (<i>t</i>) |
|---------------------------------|------------------|-----|-----|-----|------------------|
| R Postcentral gyrus | 71 | 24 | -32 | 54 | 7.40 |
| L Inferior orbitofrontal gyrus | 54 | -36 | 22 | -16 | 6.63 |
| L Rolandic operculum | 37 | -42 | 4 | 16 | 5.72 |
| R Superior frontal gyrus | 20 | 20 | -10 | 52 | 5.53 |
| L Inferior orbitofrontal gyrus | 19 | -44 | 30 | -4 | 5.42 |
| L Superior temporal gyrus | 35 | -52 | -6 | -2 | 5.39 |
| L Thalamus | 39 | -10 | -10 | 0 | 5.20 |
| L Thalamus | 73 | -16 | -22 | 12 | 5.17 |
| R Insula | 35 | 36 | 12 | 4 | 5.09 |
| R Insula | 14 | 26 | 24 | -12 | 5.02 |
| R Insula | 11 | 34 | -24 | 2 | 4.97 |
| L Middle cingulate gyrus | 10 | -12 | -6 | 46 | 4.79 |
| R Precentral gyrus | 10 | 26 | -18 | 72 | 4.77 |
| L Middle orbitofrontal gyrus | 13 | -32 | 54 | -4 | 4.75 |
| R Thalamus | 26 | 8 | -8 | 8 | 4.69 |
| R Middle cingulate gyrus | 13 | 12 | -14 | 32 | 4.66 |
| R Rolandic operculum | 34 | 62 | 6 | 6 | 4.49 |
| L Superior medial frontal gyrus | 10 | -8 | 54 | 8 | 4.42 |

Notes: $p < .001$ (uncorrected), $k = 10$.

increased brain activation between the two testing sessions was associated with decreased appetite ratings. These regions included inferior orbitofrontal cortex, thalamus, and insula, among others (see **Table 1**).

Discussion

These preliminary findings suggest that citicoline administration was associated with a modest but significant decline in appetite ratings for the group as a whole. High-dose citicoline (i.e., 2,000 mg/day) for 6 weeks was associated with a significant decline in appetite ratings from baseline, whereas no significant effect was observed for the low dose (i.e., 500 mg/day), and no changes were evident in weight status. Because the appetite effect was only significant in the high-dose group, it raises the possibility of a dose-dependent effect of citicoline on appetite suppression. Such findings are consistent with animal studies linking citicoline to increases in dopamine^{23,26} and human evidence suggesting that citicoline may be effective at reducing aspects of craving in cocaine-dependent individuals.⁹ However, given the preliminary nature of these findings and the lack of significant between-group differences in appetite suppression or weight change, further research that includes larger samples and a placebo control group will be necessary to determine the magnitude and reliability of the effects of citicoline on appetite.

Previous studies using fMRI have shown that visual perception of images of appetizing foods are generally associated with increased activation in a broad network of cortical and limbic regions, including the orbitofrontal cortex, medial prefrontal cortex, amygdala, hippocampus, ventral striatum, insula, and cingulate gyrus,^{37,38,40,42} but activation of these regions is highly dependent upon a number of factors including weight,^{40,41,48} mood,^{43,49} eating disorder diagnostic status,^{29,50} and immediate hunger or nutritional state of the individual.^{37,51,52} For the present study, we focused our analyses on three regions that are often associated with cerebral responses to food. These included the lateral orbitofrontal cortex, insular cortex, and amygdala.

In the present study, we found that citicoline administration was associated with dose-dependent changes in functional brain responses to high-calorie foods between the two visits. When compared with the low dose of citicoline, the high dose was associated with increased activation within the right lateral OFC ROI during visual perception of high-calorie foods. Medial aspects of the OFC have been associated with reward processing³² and this region tends to be activated in during perception of appetizing food stimuli.^{29,53} In contrast, activation in the lateral orbitofrontal regions has been associated with punishment experiences,³² satiety, and the desire to stop eating.^{31,43,54} When sated, images of normally appetizing foods produce increased activation of the lateral orbitofrontal cortex.⁵⁰ When considered in light of these previous studies, the present findings suggest that the high-dose treatment may have led to appetite changes by increasing the responsiveness of this region to images of calorie-rich and high-fat foods, though this speculation will require further study. High doses of citicoline were also associated with greater activation increases in bilateral insula and the left amygdala in response to the high-calorie food images. Activation of these regions has been associated with anticipation of aversive experiences and visual perception of unpleasant images in previous research,⁵⁵ and the insula has frequently been implicated in the experience and perception of disgust^{33,34} and interoceptive awareness of visceral/somatic states.³⁵ The present findings suggest that treatment with the high dose of citicoline produced significantly greater increases in left amygdala activation than the low-dose treatment. Previous research has suggested that visual perception of foods, regardless of calorie content, appears to be associated with amygdala activation.³⁸ Elevated activation within the amygdala is often associated

with negative affective experiences, such as conditioned fear⁵⁶ or perception of unpleasant or negatively valenced emotional stimuli.³³ Again, while speculative and in need of further study, these findings tentatively suggest that citicoline may affect appetite by increasing responsiveness of these regions.

Finally, it was hypothesized that change in activation of the three cerebral regions of interest between Visit 1 and Visit 2 would correlate with appetite changes over this same period. This hypothesis was supported, as increased activation within each of the three regions was significantly predictive of reduced appetite by the end of the study. In other words, appetite ratings declined most extensively for those individuals that showed the greatest increases in activation within the amygdala, insular cortex, and lateral OFC in response to high-calorie food images over the 6-week period. Findings for the insula and OFC were further confirmed in the exploratory whole brain analysis. Because activation in these paralimbic regions is often associated with negative affect,⁵⁷ aversive perceptions,^{33,34} and behavioral inhibition,⁵⁸ increased activation in these regions might indicate that the food images were being perceived as less rewarding and potentially more aversive than at baseline and therefore led to reduced desire to consume food.

Although our hypothesis was based on limited evidence that citicoline may affect the dopamine system,^{23,26-28} it is possible that the changes observed here in the high-dose group may have resulted from properties of citicoline other than its effects on the dopamine system. Citicoline has a number of mechanisms of action, including functioning as a precursor of phospholipid and acetylcholine synthesis,^{16,18} enhancement of the release of other neurotransmitters such as norepinephrine,²⁴ counteracting the buildup of β -amyloid protein and cellular apoptosis in the hippocampus,⁵⁹ and repair of neuronal membranes via increased synthesis of phospholipid components including cardiolipin⁹ and sphingomyelin.²¹ Growing evidence suggests that citicoline may have neuroprotective effects following stroke or other brain injuries and may enhance cognitive performance in patients suffering from degenerative dementias such as Alzheimer's and Parkinson's Diseases.¹⁶ Thus, the mechanisms of action and potential neural systems affected by citicoline are numerous and remain to be fully elucidated. Further research will be necessary to determine the specific appetite systems affected by citicoline and whether this compound shows clinical efficacy at changing appetite or weight status.

We present these findings as preliminary, fully mindful of the limitations inherent in a non-placebo controlled design with a relatively small sample size. Furthermore, because this was an open label trial and participants were aware of the treatment and dosage they received, it is possible that their expectations may have affected their responses to the questionnaires or the stimuli. Future studies would benefit from the use of double blind crossover designs and these findings will need to be replicated with larger samples. It should also be reiterated that despite the decline in appetite ratings, no change in actual weight was noted. However, it is possible that the change in appetite was gradual and that a 6-week trial may not have been adequate to be expressed in changes in weight. Trials extending for longer durations may clarify this issue. An additional factor to be considered is the potential influence that body mass may play in the effects of citicoline on brain responses, as previous research suggests that body mass is related to brain responses to food images.⁴¹ BMI was not controlled or manipulated in the present study because of the small sample size and limited degrees of freedom, but future investigations should consider the role of this variable in food perception. To avoid the effects of hunger on brain activation, no attempts were made to restrict food intake before the scans, but this may have also had some effect on brain responses. Future studies will need to examine the interaction of citicoline and hunger on brain responses to food stimuli. Finally, it is not possible to rule out exposure and habituation effects in the present study, as participants viewed the same stimuli on both occasions. However, this is unlikely in light of the 6-week intervening period between the scans and our finding that most participants, particularly those in the high-dose group actually showed increased activation rather than a reduction, arguing against habituation to the food stimuli. In light of the numerous neuroprotective and health promoting effects, high tolerability, and low side-effect profile of citicoline, these tentative findings are intriguing and warrant further research into the efficacy of this substance as a potential supplement for modulating appetite.

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