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Amphetamine alters neural response to sucrose in healthy women

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ABSTRACT

Amphetamine, likely via action on the brain's dopaminergic systems, induces anorectic eating behavior and blunts dopaminergic midbrain activation to rewards. Past work has hypothesized that this blunted reward responsivity is a result of increasing tonic over phasic DA activity. We sought to extend past findings to sweet taste during fMRI following single-blind administration of dextroamphetamine and placebo in 11 healthy women. We hypothesized that neural response in both limbic and cognitive sweet taste circuits would mirror past work with monetary rewards by effectively blunting sweet taste reward, and 'equalizing' it's rewarding taste with receipt of water. Behavioral results showed that amphetamine reduced self-reported hunger (supporting the existence of amphetamine anorexia) and increased self-report euphoria. In addition, region of Interest analysis revealed significant treatment by taste interactions in the middle insula and dorsal anterior cingulate confirming the 'equalizing' hypothesis in the cingulate, but unlike monetary reinforcers, the insula actually evinced enhanced separation between tastes on the amphetamine day. These results suggest a divergence from prior research using monetary reinforcers when extended to primary reinforcers, and may hint that altering dopaminergic signaling in the insula and anterior cingulate may be a target for pharmacological manipulation of appetite, and the treatment of obesity.

1. Introduction

In both children and adults, obesity has had a steadily increasing prevalence for the past several decades and has become one of the largest public health issues in modern society. Successful pharmacological treatment of obesity has remained highly elusive, which likely has limited the impact of drug-based interventions in preventing obesity related health problems. In comparison, amphetamine is one of the most successful classes of anorectic drugs currently in existence. Although chronic use of amphetamines as a pharmacological treatment for obesity is clearly problematic, a better understanding of the underlying mechanisms enabling such successful appetite suppression could provide a pathway to develop more effective medications without amphetamine's adverse side effects. The current work is the first to the author's knowledge to investigate amphetamine's effects on neural response to a rewarding sweet taste in humans, which we believe may be a useful starting point in translating animal research on amphetamine's potent appetite suppression effects to human subjects.

Dextroamphetamine sulfate (dAMPH) is the dextro-isomer of the compound d,l-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. dAMPH is considered a very successful anorectic agent (Foltin et al., 1995), and is thought to fundamentally affect reward discrimination (Schultz, 2011), a factor which may relate to it's poorly understood anorectic effects. Positron Emission Tomography (PET) studies with dAMPH during [18F]fallypride scans indicate increased dopamine concentrations in both striatal and extrastriatal regions of the brain including medial orbital frontal cortex (OFC), cingulate, precuneus, amygdala, and hippocampus (Dropley et al., 2008; Riccardi et al., 2006). Moreover, PET studies implicate gender-specific effects following dAMPH administration (Riccardi et al., 2011), highlighting the importance of careful control of potential gender differences when experimentally administering dAMPH.

To our knowledge, no studies have used fMRI to investigate the

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effects of dAMPH on reward responsivity to primary reinforcers in humans. Because food reward is complex, we used the response to a sweet taste as a simplified model of one aspect of eating behavior that aligns nicely with prior work done with monetary rewards (Knutson et al., 2004). As described in Kaye et al., (Kaye et al., 2009), sweet taste perception starts with the tongue, and is carried to the nucleus of the solitary tract by cranial nerves 7, 9, and 10, with some projections directly leading to the thalamus (Small, 2010). From the thalamus, taste processing is thought to flow through both a ventral (limbic) network of regions including the amygdala, insula, ventral striatum, ventral anterior cingulate cortex (vACC), and orbital frontal cortex (OFC), as well as a dorsal (cognitive) network that includes the hippocampus, dorsal ACC (dACC), dlPFC, and parietal cortex. This ventral network is thought to play an important role in determining the rewarding aspects of homeostatic appetitive needs, whereas the dorsal network is thought to mediate cognitive functioning such as planning and inhibition.

As a result of this paper being the first of it's kind, we turned to both animal research on dAMPHs effects on reward responsivity, and past work combining fMRI, dAMPH, and responsivity to monetary rewards to form our hypothesis. Research in baboons has hinted towards a potential sensitization towards sweet reward following amphetamine consumption (Foltin, 2011), which may contribute to the decreased eating durations and resultant anorexia. In addition, there is evidence that dAMPH may encourage alterations in eating behavior specifically via the D1 subtype of dopamine (Gilbert and Cooper, 1985), which has high cortical and subcortical concentrations in both the cognitive and limbic taste pathways (Hurd et al., 2001). Amphetamine administration has been shown to have both an inhibitory and excitatory effect on reward thresholds depending on the specifics of the experiment, and seems to be dependent on dopaminergic systems despite dAMPH acting on both noradrenergic and dopaminergic systems (Coelle et al., 1988). Self-stimulation of the lateral hypothalamus in the rat only follows administration of the d-amphetamine isomer (which acts on both dopaminergic and noradrenergic systems) and not l-amphetamine isomer (which acts only on noradrenergic systems), and is most potently modulated when directly infused into the nucleus accumbens which is a primary afferent of dopaminergic cell bodies in the ventral tegmental area (Coelle et al., 1988). In humans, dAMPH has been shown to reduce reward *anti*cipation activation in the nucleus accumbens, and serves to essentially 'equalize' reward and punishment anticipation (Knutson et al., 2004). We reasoned that neural response in both limbic and cognitive sweet taste circuits would mirror past work with monetary rewards by effectively blunting sweet taste reward, and 'equalizing' it's rewarding taste with receipt of water.

2. Methods

2.1. Participants

Eleven right-handed, healthy women with normal or corrected to normal visual acuity aged 22–40 were recruited through local and national advertisements or via previous study participation. Exclusion criteria included: past history of alcohol or drug abuse or dependence 3 months prior to the study; any medical or neurologic concerns; and any conditions contraindicative to magnetic resonance imaging. All participants underwent diagnostic and clinical assessments by a board-certified psychiatrist or psychologist using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) to ensure the absence of any Axis I diagnosis. No participants had any history of past or current drug abuse or dependence, and all participants had no use of either psychoactive medication or tobacco 3 months prior to the study. Participants additionally were required to have had a stable body weight (between 90% and 120% of ideal body weight defined as 45.5 kg +2.3 kg for each inch over 5 feet) since puberty to further establish the absence of any eating related disorder. Based on previous work showing that menstrual phase can affect response to amphetamine (Justice and de Wit, 1999), we attempted to schedule all participants to complete their fMRI sessions within the first 10 days of the follicular phase of the menstrual cycle, however, two participants were in the final one or two days of the luteal phase when the first scan took place due to slight unforeseeable cycle variations. Participants had a mean age of 26.5 (4.9SD), were all right handed, had a current BMI in the normal range (mean 22.03; 1.3SD), and ranged in educational level between 12 and 19 years (mean education 15.8; 1.9SD). The study was conducted according to the institutional review board regulations of the University of California, San Diego, and all participants gave informed consent. All eleven recruited participants completed the study, and were included in analysis.

2.2. Experimental Design

Participants performed a taste task developed at UCSD (Frank et al., 2003; Oberndorfer et al., 2013; Wagner et al., 2008) during fMRI scanning on two visits 24 h apart. Participants were informed that they would receive a dose of either dextroamphetamine sulfate (dAMPH) or a placebo (PLAC) on day one of the study, and that they would receive the dose they had not yet received on day two. In keeping with a single blind format, PLAC was always administered on day one of the study, whereas, dAMPH was administered on day two. All participants had completed prior scans at the UCSD neuroimaging center so as to reduce any confounding anxiogenic effects of undergoing scanning that may change between sessions. Scans were held on consecutive days due to many participants travelling to participate, as a result, PLAC was always administered on the first day to ensure that there was not a carry-over effect of dAMPH due to the close succession of drug conditions. Upon arrival 3 h prior to scanning each day, participants consumed a standardized breakfast and ingested either dAMPH or PLAC, this timing was employed to ensure peak response to the orally ingested AMPH (typically between 2.5 and 3.5 h) would occur while the participant was in the scanner (Asghar et al., 2003). During the course of the study, participant's heart rate, blood pressure and behavior (via several self-report measures) were measured periodically throughout the day to ensure no negative reactions to the drug, though blood glucose in response to the meal was not measured so variations in this cannot be ruled out as a confound.

2.3. Oral amphetamine administration

Dextroamphetamine sulfate was ordered and dispensed by the UCSD pharmacy. Subjects received dAMPH doses based on their individual weight, approximately 0.5 mg/kg (in 2.5 mg increments). This dAMPH dose was chosen based off prior neuroimaging work with dAMPH finding this to be an ideal dose for enhanced effects of the drug, while maintaining as little side effects as possible (Agrist and Sanfilipo, 2001).

2.4. Taste solution delivery

During the taste task, subjects were presented with two different stimuli: a 10% sucrose solution (Fisher Scientific, USA), and distilled water (Evian). Past literature has described these solutions as pleasant and neutral, respectively (Drewnowski et al., 1987). Participants received 1-mL of either the sucrose solution or the distilled water from a semi-automatic programmable

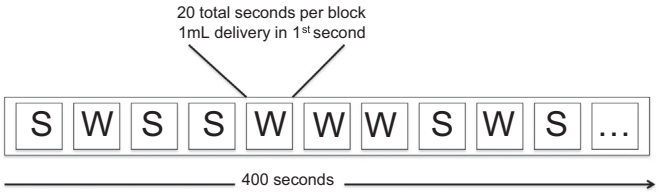

Fig. 1. Schematic of taste paradigm. On each day, participants completed two runs each of a 400 s duration containing 20 taste stimulations each of 20 s duration with only the first 14 s included in the GLM model. While participants kept their eyes closed, taste stimulation occurred for the first second, which was followed by a tongue swish and swallow that was trained to reduce motion, followed by rest until the next stimulation. Each run contained both sucrose (S) and water (W) stimulation in a pseudorandomized order that changed for each run within each drug condition.

customized syringe pump (J-Kem Scientific, St. Louis, MO) in 1-mL per second stimulations to the buccal region every 20 s, for a total of 40 samples. Two fMRI runs of 400 s each were performed during each drug condition, with each run containing 20 pseudorandom taste trials (for schematic see Fig. 1). Scanning was split into two separate runs to minimize participant discomfort and movement. Participants were trained to perform one swift tongue motion to swish the solutions across the tongue to wash the taste stimulus around the mouth, and stimulate taste buds simulating past taste studies (Frank et al., 2003). Participants were instructed to remain still with their eyes closed during the paradigm to reduce visual distractions.

2.5. Apparatus

The different macronutrient solutions were contained in two 25 mL syringes, which were attached to a semiautomatic and programmable customized syringe pump (J-Kem Scientific, St. Louis, MO), positioned in the scanner control room (Frank et al., 2003). Taste stimulation was delivered to participants via two separate approximately 10-m long FDA approved food grade Teflon tubes (Cole-Parmer Vernon Hills, IL). The syringes were also attached to a computer-controlled valve system, which enabled the two solutions to be delivered independently along the tubing. Taste delivery was controlled by E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) software operating on a PC positioned in the control room. Initialization of the E-Prime script controlling timing of stimulus delivery was manually synchronized with MR scanning by starting both sequences simultaneously.

2.6. Behavioral measures

Periodically throughout both days, participants were asked to provide subjective ratings of several different aspects of behavior (hunger, irritable, anxious, confused, euphoric, fatigued, and restless) ranging from 0 (not at all) to 7 (extremely) for the purposes of both monitoring participant status, and follow-up behavioral correlations. In addition to completing these assessments for the duration of the active effects of the drug, participants were asked to complete these ratings right before, during, and right after each scan. These three scores were then averaged to get a generalized scan time rating of how the participant felt for subsequent analysis.

2.7. MRI acquisition

Functional images were acquired in the sagittal plane using T2* weighted echo planar imaging (EPI) (Ogawa et al., 1992). Imaging data was collected on a 3T Signa Excite scanner (GE Medical Systems, Milwaukee, WI) (TR=2000 ms, TE=30 ms, flip angle=80°, 64 × 64 matrix, ASSET factor=2, 40 2.6-mm ascending interleaved axial slices with a 0.4-mm gap, 200 volumes). The first four volumes of each run were discarded so as to discount T1 saturation. EPI-based field maps were also acquired to correct for susceptibility-induced geometric distortions. High-resolution T1-weighted FSPGR anatomical images (SPGR, TI=600 ms, TE=min full, flip angle=8°, 256 × 192 matrix, 170 1.2 mm contiguous slices) were obtained for subsequent spatial normalization and activation localization.

2.8. fMRI preprocessing

Functional images were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) and R statistical packages (http://www.r-project.org). EPI images were motion-corrected and aligned to high-resolution anatomical images with the AFNI script align_epi_anat. py (Saad et al., 2009). Time points containing head movements not corrected for by coregistration were censored from statistical analysis. Though motion is often a problem in taste paradigms and additionally when amphetamines are administered, we were not forced to exclude any of the 11 participants due to head motion based on our subjects ability to maintain task related motion under 3 mm. Statistical analyses were performed using a general linear model (GLM), whereby taste blocks were modeled using AFNI's SPMG function. Block signals for the sucrose and water conditions, calculated as beginning from the taste administration onset time and continuing for 14 s, were included as regressors of interest. This 14 s duration was chosen to match prior works in which the participant was also instructed to 'swish and swallow' following taste administration (Boutelle et al., 2015). The contrast between sucrose and water was also modeled at the individual subject level. A multiple regression model was used whereby regressors derived from the experimental paradigm were convolved with a prototypical hemodynamic response function (HRF) (AFNI: waver). Six motion parameters (3 rotations and 3 translations) were additionally used as nuisance regressors to account for motion artifact. Registration to the MNI-152 atlas was performed using FMRIB's Non-linear Image Registration Tool (FNIRT), part of FSL (http://fsl.fmrib.ox.ac.uk/fsl/). Functional data were scaled to percent signal change (%SC) and smoothed with a 4.2 mm FWHM Gaussian kernel. The %SC map for each individual was visually inspected for outliers before inclusion in group-level analyses.

2.9. Regions of interest

The selection of our regions of interest (ROIs) was based on prior review articles examining the circuitry involved in gustatory processing and perception (Kaye et al., 2009; Volkow et al., 2011). The anorectic effects of dAMPH have been well observed in both human (Foltin et al., 1995), and animal studies (Asin et al., 1992). We wanted to follow this gustatory circuitry when participants were given dAMPH to see where sweet taste could be altering an individual's experience of gustatory stimuli when compared with a non-caloric solution (water). Our insula, thalamus, dorsal lateral prefrontal cortex (DLPFC), amygdala, parietal, and dorsal anterior cingulate (ACC) ROIs were derived from the Harvard-Oxford Atlas (Desikan et al., 2006). Our parietal, amygdala, and thalamus ROIs were all directly extracted from the Atlas without modification, and were included due to their involvement in the limbic and cognitive gustatory neurocircuits laid out in Kaye et al., (Kaye et al., 2009). To obtain a dorsal ACC ROI, the ACC was subdivided into rostral and dorsal subcomponents by drawing a 45-° line from the anterior commissure in line with Bush et al.'s functional segregation of the cingulate (Bush et al., 2000). We included the entire insula cortex due to prior work indicating that the different

subdivisions of the insula work as an integrated sensory region (Small, 2010), with the more somatic aspects occurring in the posterior regions becoming increasingly integrated as you move anterior (Craig, 2009). We attempted to additionally include an orbital frontal cortex (OFC) ROI, but difficulty imaging this region resulted in significant signal dropout unfortunately making data from this region unreliable. The anterior ventral striatum (STR) ROI was defined a-priori based upon known functional distinctions (Martinez et al., 2003) to include the nucleus accumbens extending into the rostroventral caudate and ventrolateral putamen, and also comprising the anterior caudate and anterior putamen. Using the anterior commissure in the coronal plane, the caudate nucleus and putamen were sliced into anterior and posterior subdivisions and only the anterior subdivisions were retained for analysis. This striatum ROI was included due to this region's involvement with the rewarding properties of food, the dorsal striatum was not included due to it's perceived role in maintaining caloric needs for survival, a function not likely applicable to this paradigm when subjects are not fasted (Volkow et al., 2002).

2.10. Statistical analysis

Paired samples *t*-tests were used to compare changes in the average of the self-report measures collected immediately before, half-way through the scan, and immediately following the scan in response to the dAMPH challenge via the t.test function in R statistical software.

For the fMRI data, a linear mixed effects (LME) analysis in R was performed for each voxel within the left and right insula, thalamus, DLPFC, dorsal ACC, amygdala, parietal lobe, and striatum ROIs specifically investigating the interaction between drug and condition. ROI main effects of drug and condition were not pursued due to the potentially cumulative negative effects of their lack of relevance to the impetus of the study, however, whole-brain main effects of drug and taste stimuli can be found in the supplementary materials (Table S1, S2). Subject was treated as a random effect, with drug (AMPH, PLAC) and condition (sucrose, water) as within subject factors. Small volume correction was determined using Monte-Carlo simulations (via AFNI's 3dClustSim) to guard against false positives. To achieve an a posteriori ROI-wise probability of $p < 0.05$, an a priori voxel-wise probability of $p < 0.05$ in a cluster of 232 μL with 29 connected voxels (faces touching) in each insula ROI was required, a cluster of 264 μL with 33 connected voxels in each parietal ROI was required, a cluster of 312 μL with 39 connected voxels in the left DLPFC and 320 μL with 40 connected voxels in the right DLPFC was required, a cluster of 136 μL with 17 connected voxels in the left amygdala and 144 μL with 18 connected voxels in the right amygdala was required, and a cluster of 200 μL with 25 connected voxels in the left striatum and a cluster of 208 μL with 26 connected voxels in the right striatum was required. Post hoc analyses were conducted using Tukey's HSD. T -values were obtained by running voxel-wise post-hoc analysis within each ROI and returning the t-value from the peak voxel from each significant cluster as obtained from the previously run LME. These tests were run to statistically verify directionality as seen in the graphs of the significant cluster outputs from the LME. Inspection of the data indicated an outlier with strongly flipped responses in the insula when compared with the rest of the group, we re-analyzed ROI LMEs with the outlier removed and F-values increased ($F(1,20) = 14.75$ with; $F(1,18) = 17.44$ without). We left this participant in subsequent analysis to avoid reducing statistical power since this participant was not driving significance.

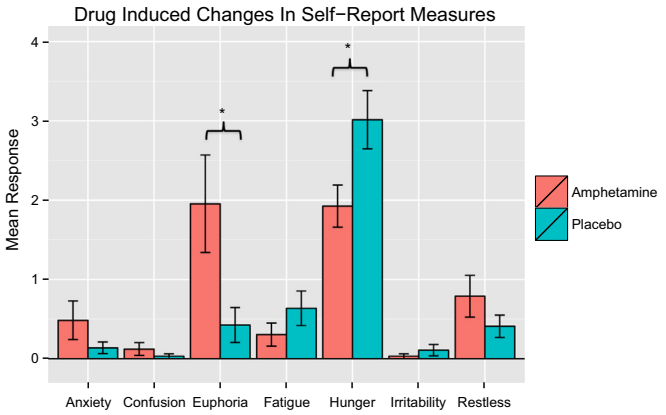

Fig. 2. Administration of Amphetamine was associated with increased self-reported euphoria ($t = 2.6158$, $DF = 10$, $p = 0.02578$), and decreased self-reported hunger ($t = 2.6529$, $DF = 10$, $p = 0.02419$) at the time of scanning when compared to Placebo. Error bars indicate standard error of the mean.

3. Results

Paired samples *t*-tests performed on the changes in self-report measures in response to the administration of dAMPH are shown in Fig. 2. Of the recorded self-report measures, there was a significant decrease in self-reported hunger ($t = 2.6529$, $DF = 10$, $p = 0.02419$) in response to dAMPH, and there was also a significant increase in self-reported euphoria ($t = 2.6158$, $DF = 10$, $p = 0.02578$) in response to dAMPH administration. These findings support the notion that the chosen dose of dAMPH given to participants was large enough to ensure at least a minor form of self-reported amphetamine anorexia, while not being so large as to affect various other aspects of well-being.

The ROI analysis revealed a significant drug x taste condition interaction in the right middle insula ($p < 0.05$, $F(1,20) = 14.75$; MNI XYZ = 42, −8,6; Fig. 3.). Post-hoc *t*-tests indicated that this interaction was driven primarily by increased right middle insula responsivity to sucrose when compared to water on the amphetamine day ($t = 4.0368$), with this difference being reversed on the placebo day ($t = -1.3941$). In addition, there was also a significant drug x taste condition interaction in the left dACC ($p < 0.05$, $F(1,20) = 12.56$; MNI XYZ = −2,4,28; Fig. 4.). Post-hoc *t*-tests indicated that this interaction was primarily due to increased left dACC response to sucrose when compared to water on the placebo day ($t = 4.0368$), with this difference being slightly reversed on the amphetamine day ($t = -0.5663$). It is important to note that the signal change in the dACC is negative in these interactions, making this increased response to sucrose on the placebo day actually a reduced deactivation. Prior work has suggested that there is a globally distributed effect of dAMPH on both cerebral blood flow and metabolism (Kahn et al., 1989). The specificity of the drug by condition effects to the insula and dACC with no effects in the other investigated ROIs implies these results likely do not simply reflect any general neurovascular effects of dAMPH.

4. Discussion

To our knowledge, this is the first study to examine the BOLD response to sweet taste reward and to explore how appetite and gustatory neurocircuits may be changed by dAMPH in healthy women. Our results show that the acute administration of dAMPH led to self-reported amphetamine anorexia as evidenced by decreased hunger ratings despite being fed the same meal prior to scanning on both days. In line with our primary hypothesis, dAMPH was associated with an 'equalizing' effect when comparing

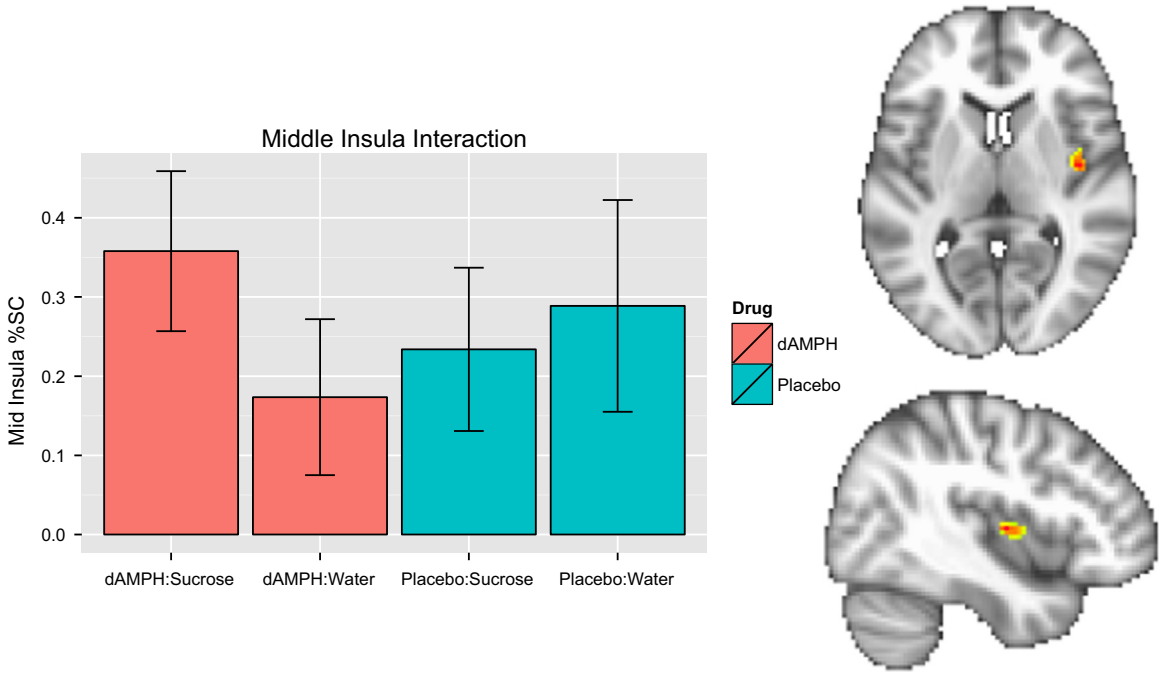

Fig. 3. There was a significant drug * taste interaction in the right middle insula ($p < 0.05$, $F(1,20) = 14.75$). Post-hoc *t*-tests indicate that this interaction was driven primarily by increased right middle insula responsivity to sucrose on the amphetamine day ($t = 4.0368$) that was attenuated and actually flipped on the placebo day ($t = -1.3941$). Error bars indicate standard error of the mean percent signal change.

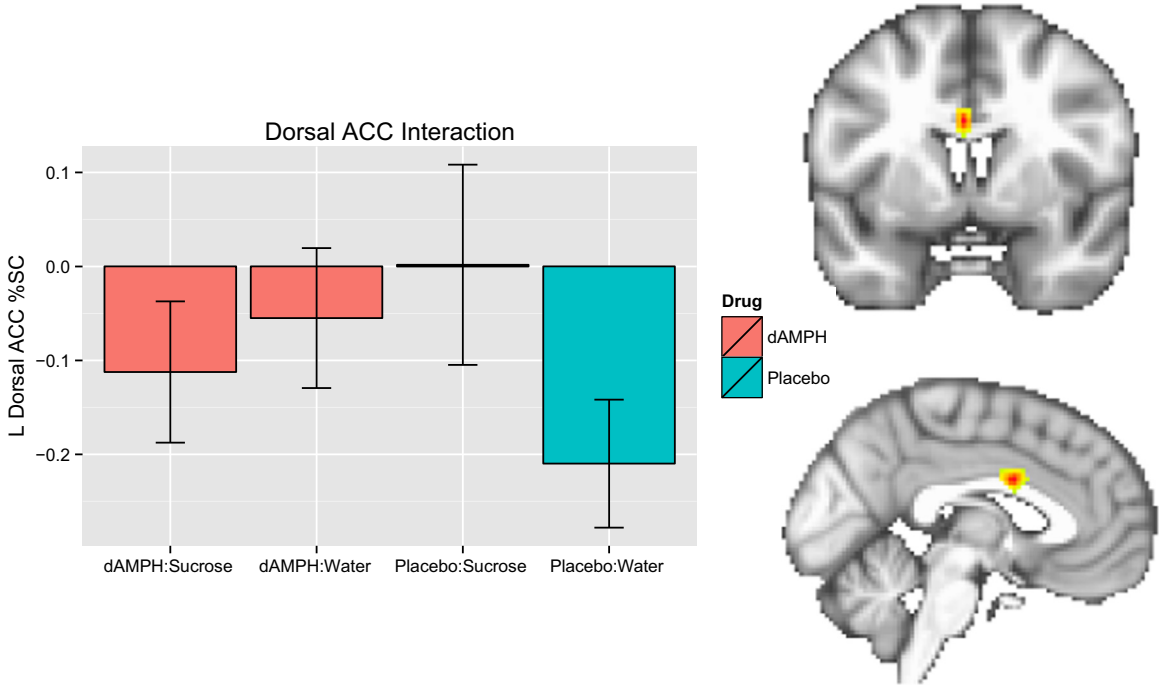

Fig. 4. There was a significant drug * taste interaction in the left dorsal anterior cingulate ($p < 0.05$, $F(1,20) = 12.56$). Post-hoc *t*-tests indicate that this interaction was driven primarily by left dorsal anterior cingulate hypo-activity to water compared to no %SC change to sucrose on the placebo day ($t = 4.445$), a pattern that was actually flipped on the amphetamine day ($t = -0.5663$). Error bars indicate the standard error of mean percent signal change.

BOLD response to sweet taste reward and receipt of water in the dorsal ACC. Contrary to our hypothesis, however, dAMPH was associated with further separation between BOLD response to receipt of sucrose and water in the limbic system, specifically the insula, with no relationship in the other cognitive ROIs examined. This differential pattern of response to sucrose relative to water during the dAMPH day in the limbic and cognitive system, though counter to our initial hypothesis, may be a the neural manifestation for the mechanism by which dAMPH leads to amphetamine anorexia, and may be a manner in which sweet taste reward diverges from response to monetary reward as seen in past research. Perhaps the sensitization effects dAMPH has previously been shown to have on consumption of sweet foods is partially due to an over-active limbic system in response to rewarding taste stimuli, and this over-active limbic circuit, combined with a hypo-active cognitive circuit may somehow combine to lead the individual to feel satiated faster than under normal conditions, though we feel this is plausible, this is merely speculative.

This work provides an extension to humans from the dominance of animal models inquiring how dAMPH affects food reward. However, there is a considerable animal literature to which these results can be compared. Pharmacologically, dAMPH was originally thought to instigate anorexia by affecting all or some of these 3 catecholamines: serotonin, dopamine and norepinephrine. There is considerable evidence, however, that serotonin does not play a role in the anorectic effects due to the perseverance of amphetamine anorexia following both electrolytic and radio frequency lesions of the raphe nucleus (Samanin et al., 1972; Carey, 1976). There is, however, considerable evidence that both dopamine and norepinephrine do play a role in the anorectic effects of dAMPH, though the research emphasis has been primarily on dopamine. Dopamine is thought to be an integral aspect of the anorectic effects of dAMPH in part due to animal research implicating that the administration of Primozide, a typical neuroleptic and dopamine antagonist, was able to counteract the anorectic effects of amphetamines, and Apomorphine was able to potentiate the anorectic effects though it's action is paradoxically suppressing mesolimbic dopamine neurons (Towell et al., 1988). Using pharmacological manipulations that target specific subtypes of dopamine, there is evidence that it is the D1 receptor subtype, not the D2 subtype, that may be responsible for the dopamine mediated anorectic effects of dAMPH (Gilbert and Cooper, 1985). In addition to dense D1 innervation in subcortical structures, cortical D1 is overwhelmingly represented in the dACC and insula (Hurd et al., 2001), which fits in well with our results primarily implicating these two structures in dAMPH's effect on sweet taste. Though the current results do seem to fit well with dAMPH based D1 changes shown previously, the use of fMRI in the current study does not enable investigation of specific neurotransmitters making these associations again purely speculative.

The relationship between D1 and amphetamine anorexia has a complicated and seemingly conflicting story in the literature. As mentioned, there is evidence that selective D1 antagonism is sufficient for reversing the anorectic effects of amphetamine (Gilbert and Cooper, 1985), however, recent evidence has implicated that food intake increases D1 activity of the dACC and that photostimulation of D1 in the dACC increases feeding, with inhibition of D1 neurons decreasing intake (Land, 2014). These dACC D1 neurons were shown to have the basolateral amygdala as a primary downstream target of these afferents, which also induced an increase in feeding when photostimulated, further implicating the role of increased D1 activity in the dACC in increasing feeding (Land, 2014). These results, though seemingly conflicting with D1's role in dAMPH induced anorexia, is consistent with the apomorphine enhancement of amphetamine anorexia (Towell et al., 1988). Furthermore, there is evidence in rats that electrolytic lesions of the dorso-medial amygdala attenuates the anorectic effects of amphetamines (Cole, 1978) which despite it's location in a separate locus of the amygdala may support this dACC top-down network proposed in Land et al. (2014). Our results are in line with this proposed mechanism due to the current work showing drug x taste condition interactions in the dACC following the consumption of dAMPH. The current work combining amphetamine anorexia, sweet taste, and fMRI parallels prior work combining fMRI with pure taste stimuli showing a taste invariant drop in anterior cingulate response when sated (Haase et al., 2009).

In addition to the findings in the dorsal ACC, in the current work we saw dAMPH altered mid/posterior insula response to sweet taste. Though the primary gustatory cortex is traditionally conceptualized as being slightly anterior to the current cluster, the insula is often thought of as an interoceptive center that receives lower-level sensory input in the posterior regions, and integrates as you move anterior (Craig, 2009). The insular cluster found in the current work being posterior to the primary gustatory cortex leads the authors to believe that this may be representative of some form of a lower-level sensory processing, though this is merely speculative. Interestingly, work in rats has implicated a peripheral locus for amphetamine anorexia, in which visceral sympathetic denervation by coeliac ganglionectomy protected mice from the anorectic effects of dAMPH (Tordoff et al., 1982). Though attributing the localization of this change in BOLD to the posterior insula to a neural representation of the peripheral response of the viscera is not something the current study is able to address, we think this could be a fruitful area for future research.

There were several limitations of note in this study. First, the relatively small number of subjects is likely limiting power, and may have enhanced signal dropout further hindering our ability to examine the OFC. In addition, the fixed order of drug administration leaves this dataset open to potential order effects on the behavioral and neural responses due to a potential systematic deblinding of the subject as to which day they received dAMPH. It should also be noted that the current work contained solely female participants, which may limit generalizability to the population at large. Finally, self-reported hunger was used as a proxy for amphetamine anorexia, methodologically this should be improved in future works by measuring actual consumption to quantify amphetamine anorexia. Future works should measure not only change in hunger, but also changes in the self-reported pleasantness of the sweet taste stimulations so this can be in turn related to alterations in the BOLD response changes. Finally, due to the low power of this study, brain-based changes were not seen to be significantly associated with behavioral changes once multiple comparisons were accounted for which limits the interpretability of the observed findings. Despite these potential limitations, these novel data support the likelihood that the powerful anorectic effects of dAMPH may be working to alter response to sweet taste by cortically altering responses in the insula and dorsal ACC. Furthermore, by potentially targeting these regions, pharmacologically induced appetite suppression may be able to reproduce the anorectic effects of dAMPH.

Conflict of interest

The authors have no conflicts to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2016.04.017.

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