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Electroretinographic detection of human brain dopamine response to oral food stimulation

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Abstract

The activity of dopamine-dependent retinal signaling can be assessed using electroretinography. We postulated that response of this system to oral food stimulation might provide accessible insight into the brain dopamine response to oral stimuli as retinal dopamine concentration is dependent upon mid brain dopamine concentration. Nine individuals had cone ERG (b wave) response to oral food stimulation and oral methylphenidate (MPH) administration measured on separate days, and completed self reported eating behavior questionnaires. We found significant and similar increases in b wave response to both stimuli ($p = 0.012$ and $p = 0.042$, MPH and food respectively) and significant correlations of the food stimulated b wave amplitude with binge eating related behavior as measured by the Gormally Binge Eating Scale ($r = 0.68$, $p = 0.044$) and self-reported trait hunger as measured by the Stunkard and Messick Three Factor Eating Questionnaire ($r = 0.67$, $p = 0.048$). The significant increase in food stimulated dopamine dependent b wave amplitude and correlation with methylphenidate stimulated b wave amplitude suggest that ERG may offer a relatively inexpensive and accessible methodology for potentially assess dopaminergic responses to food and other externally applied stimuli that have been implicated in the pathogenesis of a number of human diseases.

Introduction

The assessment of central dopaminergic activity is of great interest for many research work streams. However, the need for time-demanding, technically-challenging, and costly imaging procedures has limited its pursuit. Here we suggest that electroretinography (ERG), a relatively inexpensive (Medicare reimbursement is $150 per session) (1), established and widely used ophthalmologic technique, whose output is dependent upon signaling of the dopamine circuitry of the retina (2), has the potential to be used to assess response of dopamine circuits within other regions of the brain to externally applied stimuli. Roy et al

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Disclosures

There were no conflicts of interest for any of the authors.

(3) demonstrated that the cone b-wave signal of the ERG is positively correlated with spinal fluid dopamine metabolite concentration and that spinal fluid dopamine is directly dependent upon dorsal striatum dopamine concentration. Based on the evidence that both sugar (4) and fat (5) consumption increase brain dopamine in rats, and that PET imaging studies in humans show dopamine release in the dorsal striatum in response to food-related visual, gustatory and olfactory cues (6), as well as to consumption of a favorite meal (7), we tested the use of ERG to assess the retinal dopaminergic response to oral food stimulation in nine individuals by measuring their cone b-wave signal. To corroborate our results we compared the dopaminergic responses to food stimulation with the dopamine responses to systemic administration of methylphenidate, a known dopamine agonist, and also correlated dopamine responses under placebo, methylphenidate and food stimuli with self-reports of habitual eating behavior as measured by the Binge Eating Scale (BES)(8) and the Three Factor Eating Questionnaire (TFEQ) (9). We hypothesized that oro-sensory stimulation with a high sugar, high fat food would increase b-wave amplitude of the ERG to the same extent as methylphenidate.

Methods and Procedures

Participants

The protocol was approved by the Institutional Review Board and HIPAA Privacy Board of St. Luke's-Roosevelt Hospital Center and all participants gave informed consent before taking part in the test sessions. Fourteen adults screened for this study. One woman was excluded for a history of eating disorders. Three men and one woman withdrew from the study for personal reasons. Four men and five women completed the study. Participants received a physical that included measurement of height and weight, a detailed medical history and comprehensive metabolic blood chemistry panel before being chosen for the study, as well as a dilated eye exam. Participants also completed validated eating behavior instruments (8, 9). Exclusion criteria included metabolic disorders such as diabetes, thyroid or renal disease, neurological disorders such as Parkinson's disease, Tourette's syndrome or a family history of Tourette's syndrome, schizophrenia, bipolar disease, current major or situational depression (Beck Depression Inventory score ≤17), current or history of anorexia nervosa or bulimia nervosa, current use of any prescription medication except for oral contraceptives, pregnancy, use of tobacco products or recreational drugs, allergies to dairy, wheat, corn or nut products. In addition, all participants were weight stable (within 10 pounds) for three months preceding the experimental sessions and were not pregnant or nursing within the last year.

Study Design

Each participant completed four test sessions in which the following conditions were presented, each on a separate day: placebo (water), 10 mg methylpheidate, 20 mg methylphenidate, food stimulus (5 grams of chocolate brownie presented 3 times). The order of presentation varied in no systematic order and was dependent upon availability of supervising physician as drug dosing could only be done when a physician was present for the whole test session. Since we were obtaining an objective measure (electrical signal of the retina) we assumed that order of stimulus presentation would not affect our study results.

Participants fasted for four hours prior to the test session. Upon arrival at the lab, they completed (during the methylphenidate sessions) a Drug Effects Questionnaire that was repeated every fifteen minutes for the first hour of the test session and then again at 90 minutes and 120 minutes. They then received a single dose of 10 mg or 20 mg of methylphenidate and had vital signs monitored for the next two hours. Forty minutes after dosing with methylphenidate, participants had their left eye treated with 0.5% proparacaine, a topical anesthetic, and dilated with 1% tropicamide and 2.5% phenylephrine. ERG, per Gouras (10) was performed 20 minutes after eye dilation. For the placebo and food conditions, the participants received no methylphenidate, had their eyes dilated, then, 20 minutes after eye dilation, either the placebo (a small sip of water) or 5 grams of chocolate brownie, was administered immediately prior to each of the 3 series of light flashes for the ERG scanning.

ERG Procedure

We utilized an LKC EPIC 2000 electroretinograph instrument system equipped with a ganzfeld stimulator (LKC Inc, Gaithersburg MD). ERG measurements were obtained either immediately after drinking water (placebo), or chewing 5 grams of chocolate brownie; or one hour after dosing with 10 mg or 20 mg oral methylphenidate. ERG measurement, per Gouras (10) involved 3 series of 200 flashes of light (450 nm) delivered over 120 seconds. The food stimulus or sip of water was delivered just prior to each series of 200 flashes. The results of these 200 flashes were averaged to produce an electroretinogram. Data from the three electroretinograms were then averaged to obtain the b wave amplitude under each test condition.

Data Analysis

Data were analyzed using PAWS, ver. 18 (Chicago, IL). The threshold of significance was set at alpha=0.05. The main outcome measure was the amplitude of the cone b-wave under the experimental conditions. Repeated Measures ANOVA was used to assess the difference between b-wave amplitude under the placebo and each methylphenidate condition separately, and under placebo and food stimulus condition. Regression analysis was used to assess the correlation of b wave amplitude between the food and methylphenidate conditions, and the correlation of b wave amplitude (under food and methylphenidate conditions separately) with BES and TFEQ scores.

Results

Four men and 4 women with BMI 32 ± 5 kg/m^2 and age 39 ± 10 years, completed all four sessions of the study. One woman completed the baseline and food stimulus sessions, but withdrew before completing the methylphenidate dosing sessions. Her data is included in the analyses of the placebo and food stimulus conditions. BES scores ranged from 3 to 19 (mean 9 ± 6), TFEQ-Hunger scores ranged from 1–8 (mean 5 ± 2), TFEQ-Cognitive Restraint scores ranged from 5 to 17 (mean 11 ± 4) and TFEQ-Disinhibition scores ranged from 2–12 (mean 6 ± 3).

We observed a significant increase in b-wave amplitude in response to the 20 mg methylphenidate dose ($F = 11.3$, $p = .012$). The increase in b-wave amplitude for the 10 mg dose was not significant ($F = 3.4$, $p = .11$). The increase in b-wave amplitude in response to oral food stimulation was also significant ($F = 5.85$, $p = .042$). Figure 1 shows a representative composite ERG scan of baseline, food and 20 mg methylphenidate conditions demonstrating an equivalent response to food and 20 mg methylphenidate. Regression analysis showed that b-wave amplitudes under these two conditions were correlated ($r = 0.87$, $t = 4.7$, $p = .005$) (Figure 2). Figures 3 and 4 show significant correlations between b-wave amplitude under the food stimulus condition and the BES score ($r = 0.68$, $p = 0.044$), and the Hunger score of the TFEQ ($r = 0.67$, $p = 0.048$), respectively. b-wave amplitude under 20 mg methylphenidate stimulus was also significantly correlated with the Hunger score of the TFEQ ($r = 0.74$, $p = 0.036$) and approached significance with the BES score ($r = 0.69$, $r = 0.057$). There were no significant correlations observed between self-reported eating behavior and the baseline (placebo stimulus) b-wave amplitude, nor were there any significant correlations observed between baseline, food stimulated and 20 mg methylphenidate stimulated b-wave amplitudes and age or BMI.

Discussion

Our data demonstrate that the ERG b wave responds to oral stimulation with a high sugar, high fat food with a magnitude equivalent to that observed with a 20 mg dose of the dopamine agonist methylphenidate. This finding implies that activity of dopamine neurons in the retina reflect brain dopaminergic activity If reproducible, this accessible methodology could greatly facilitate the screening of patients with obesity and eating disorders to quickly establish whether neurochemical aberrations in dopamine systems are part of the pathology, thus suggesting a potential target for pharmacological intervention.

Our data also demonstrate significant correlations between 1) the BES score (a measure of binge eating related behavior) and b-wave response to food, and 2) the TFEQ-Hunger score (a measure of susceptibility to hunger driven eating) and b-wave response to food that are consistent with those reported by Wang et al (11) using raclopride-labeled PET imaging. In this study Wang et al observed a significant correlation between BES score and dopamine release in the caudate, a part of the dorsal striatum of the brain, after food stimulation. We did not observe a significant correlation between the 10 mg dose of methylphenidate and the oral food stimulation condition, as was observed with the 20 mg dose of methylphenidate. This was most probably due to the plasma concentration and pharmacokinetics of each dose. Volkow et al (6) reported that an effective concentration of 0.2–1.0 mg/kg was needed to produce 50–75% occupancy of dopamine receptors by dopamine. The effective concentration for the 20 mg methylphenidate dose was 0.22 ± 0.02, which is within the effective concentration range specified by Volkow et al (6), while the effective concentration for the 10 mg methylphenidate dose was only half of that needed to produce increased occupancy of dopamine receptors by dopamine (0.11 ± 0.02 mg/kg).

Assessing the central dopaminergic response to food is instrumental in elucidating the molecular underpinnings of weight gain and potential drug targets for the treatment of obesity (12). Animal studies providing simultaneous measurement of ERG response

midbrain dopamine response to oral food stimuli are needed to validate the use of ERG as a proxy for central dopaminergic responses. If verified, ERG could provide the neurotransmitter specificity of PET at a much lower cost (1) thus offering an accessible and inexpensive methodology to assess the brain's response to a variety of stimuli implicated in the pathogenesis of a number of human diseases.

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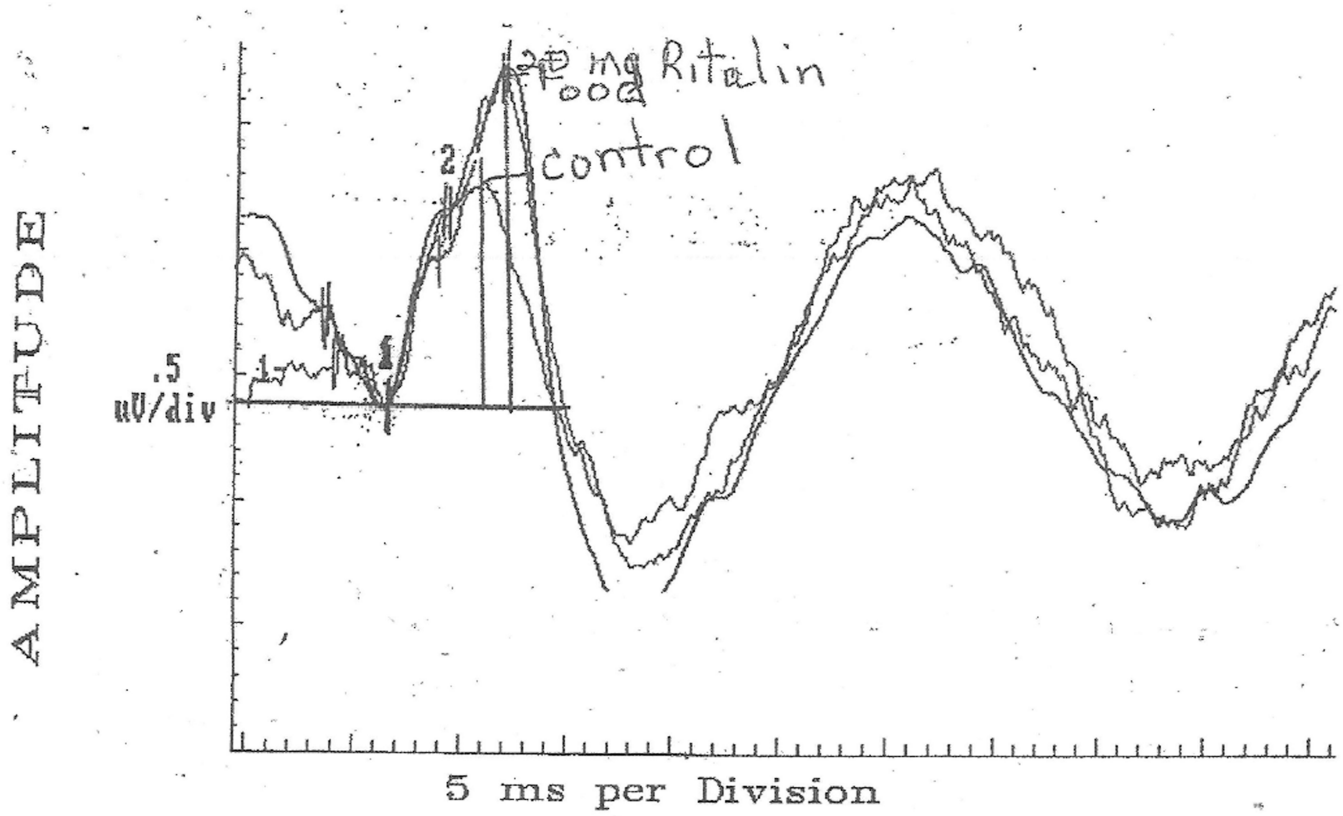

Figure 1.
Composite ERG
A composite of the ERG scans of water, food and 20 mg methylphenidate stimulation from one participant. This composite scan is representative of the b wave response observed in this study to these three stimuli.

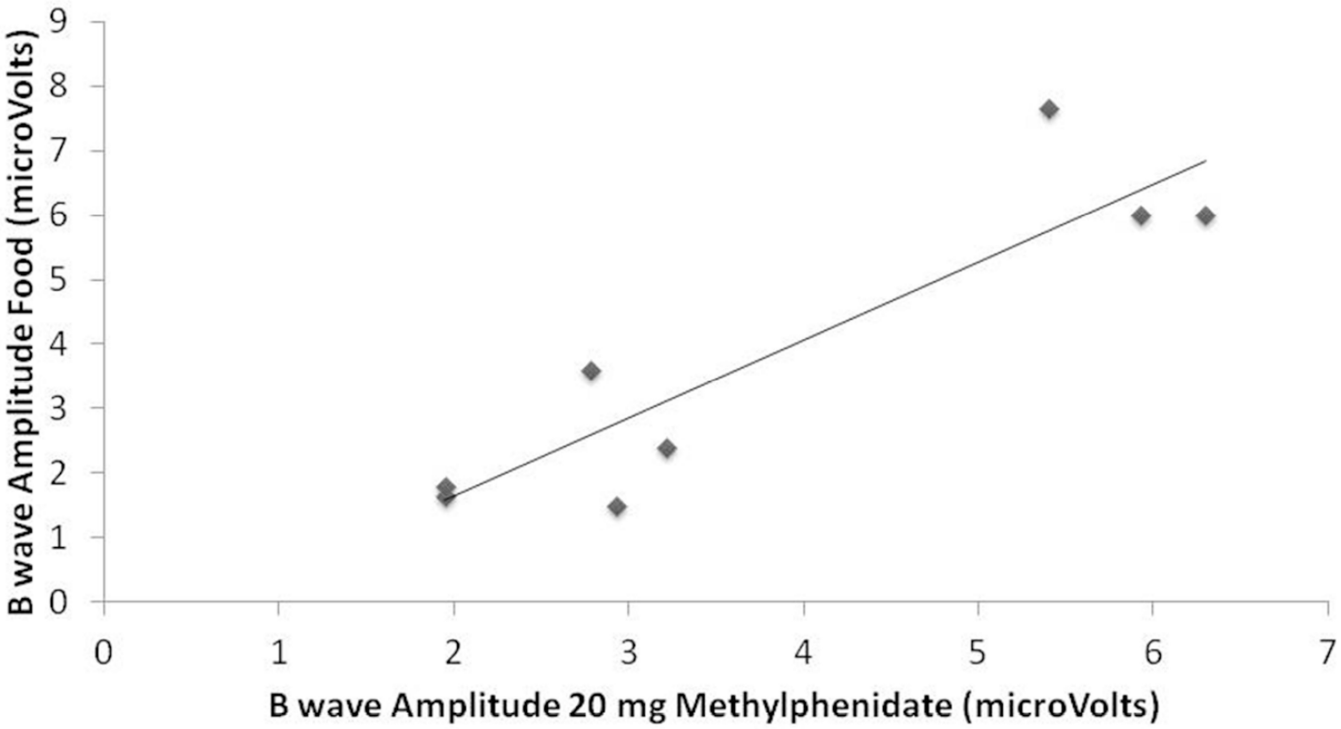

Figure 2.

Correlation of Effect of Methylphenidate and Food on B Wave Amplitude (r = 0.90, p = 0.002)

This graph shows the with-in subject correlation between the 20 mg methylphenidate stimulus and the food stimulus.

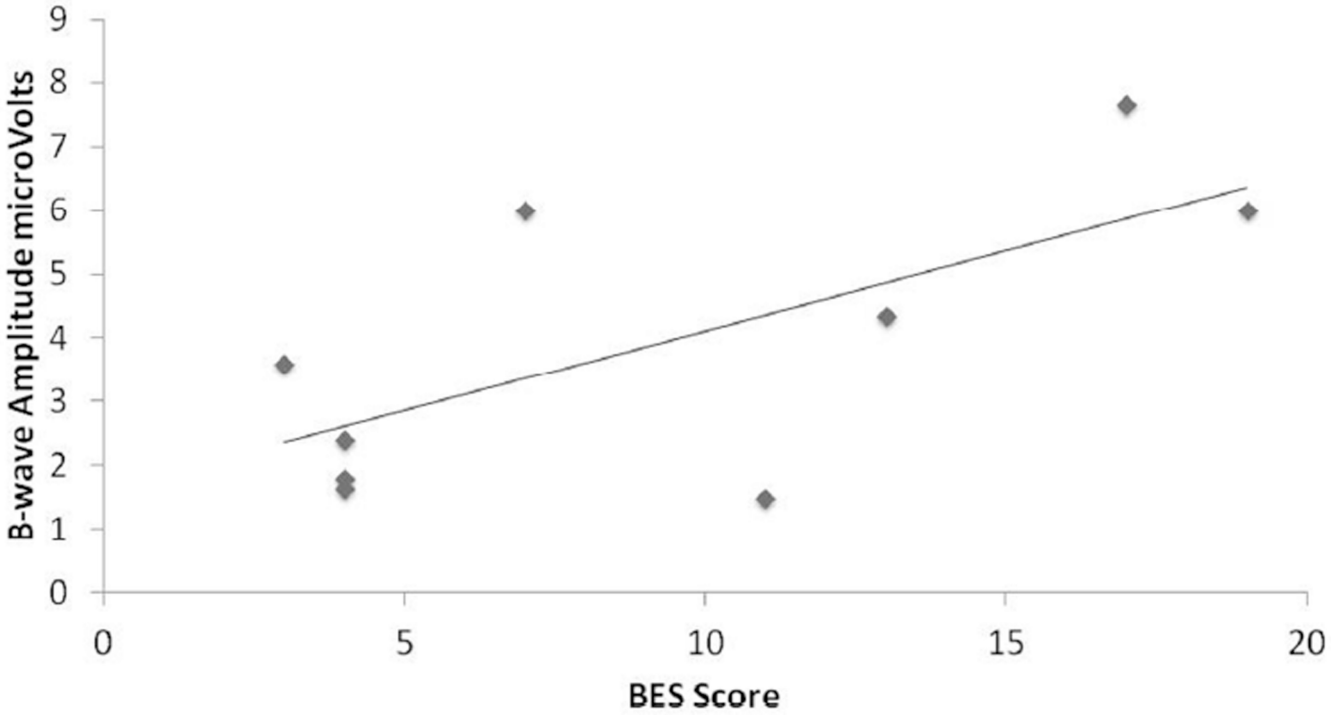

Figure 3.

Correlation of BES Score with Food Stimulated B-Wave Amplitude (r = 0.68, p = 0.044) This graph demonstrates a positive correlation between food stimulated b-wave amplitude and BES score.

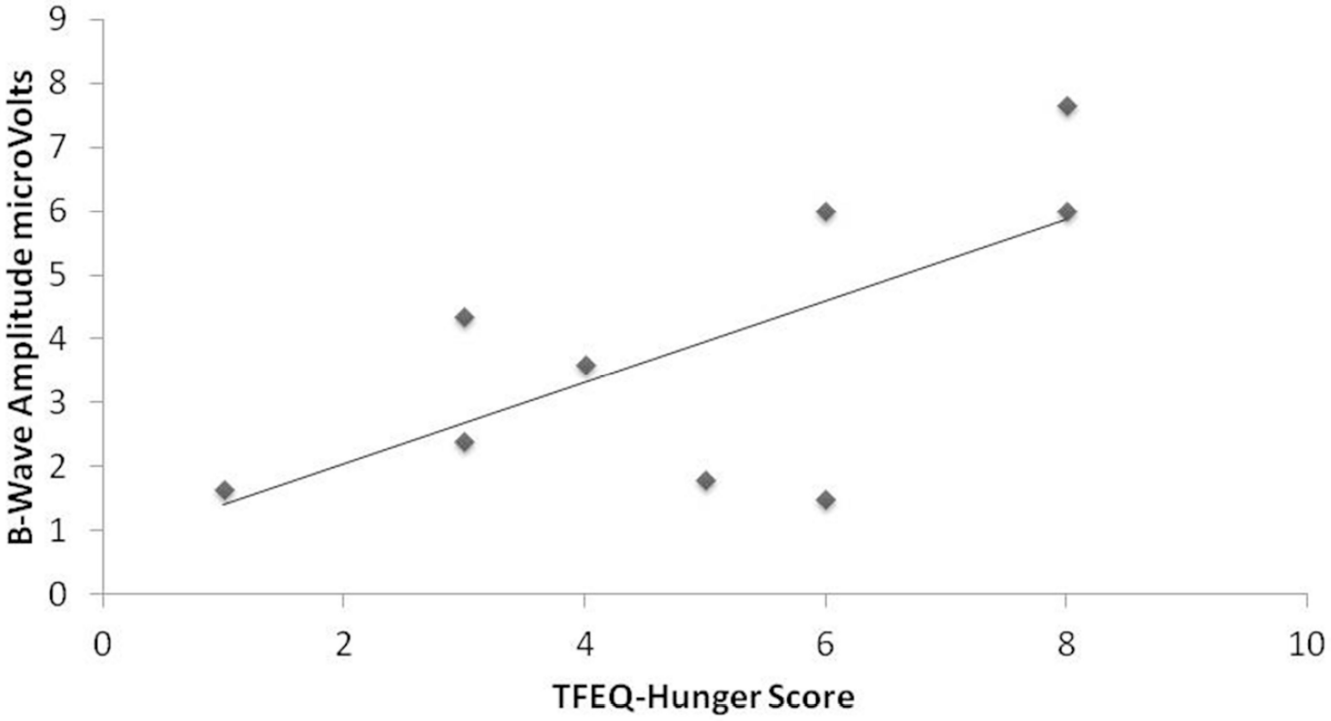

Figure 4.

Correlation of TFEQ-Hunger Score with Food Stimulated B-Wave Amplitude (r = 0.67, p = 0.048)

This graph demonstrates a positive correlation between the food stimulated b wave amplitude and the Hunger score of the TFEQ.