



# Fatty acid amide supplementation decreases impulsivity in young adult heavy drinkers



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## HIGHLIGHTS

- False alarm rate on Go/No-Go has been linked to dorsal striatal dopamine adaptation.
- OEA supplementation does not change self-reported impulsivity (BIS-11).
- OEA supplementation reduces false alarms on a Go/No-Go task in heavy drinkers.
- Improved sensitivity on a Go/No-Go task is associated with reduced alcohol intake.

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## ABSTRACT

Compromised dopamine signaling in the striatum has been associated with the expression of impulsive behaviors in addiction, obesity and alcoholism. In rodents, intragastric infusion of the fatty acid amide oleoylethanolamide increases striatal extracellular dopamine levels via vagal afferent signaling. Here we tested whether supplementation with PhosphoLean™, a dietary supplement that contains the precursor of the fatty acid amide oleoylethanolamide (N-oleyl-phosphatidylethanolamine), would reduce impulsive responding and alcohol use in heavy drinking young adults. Twenty-two individuals were assigned to a three-week supplementation regimen with PhosphoLean™ or placebo. Impulsivity was assessed with self-report questionnaires and behavioral tasks pre- and post-supplementation. Although self-report measures of impulsivity did not change, supplementation with PhosphoLean™, but not placebo, significantly reduced false alarm rate on a Go/No-Go task. In addition, an association was found between improved sensitivity on the Go/No-Go task and reduced alcohol intake. These findings provide preliminary evidence that promoting fatty acid derived gut-brain dopamine communication may have therapeutic potential for reducing impulsivity in heavy drinkers.

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## 1. Introduction

Deficient dopamine signaling has been implicated as both a cause and a consequence of obesity, alcoholism and addiction [1,2]. With respect to obesity, in rodent models a high fat diet increases adiposity, decreases extracellular striatal dopamine response to nutrients [3], decreases D2 receptor density in the striatum and increases compulsive responding for food [4]. Neuroimaging studies suggest parallel effects in humans. Overweight/obese compared to healthy weight individuals show reduced change in striatal D2 receptor binding potential in response to glucose ingestion (consistent with reduced dopamine

release) [5] and several studies have reported a negative association between body mass index (BMI) and the blood oxygen level dependent (BOLD) response to milkshake consumption in the caudate nucleus [6–8]. Although BOLD does not directly measure dopamine release, this effect is dependent upon the Taqla A1 polymorphism, which affects D2 receptor density, thus linking the BOLD response to D2 receptor signaling [6]. Consistent with the rodent work, the decreased response also appears to be a consequence rather than a cause of obesity since it is associated with weight gain [9], but not risk for obesity [10]. Finally, and critical for the aim of the current study, lower BOLD response to milkshake in the caudate nucleus is associated with increased impulsivity, especially in overweight/obese individuals [8]. Collectively these findings suggest that a diet high in fat and/or increased adiposity results in dopamine adaptations in the dorsal striatum that increase impulsive behaviors, which are themselves a risk-factor for obesity [11].

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**Table 1**  
Subject anthropometric & demographic data of two groups based on intake measures.<sup>a</sup>

	PhosphoLean (n = 11)	Placebo (n = 11)	p-Value
Age (years)	27.3 ± 7.89	25.3 ± 4.35	0.47
Male sex (n,%)	7 (63.6%)	6 (54.5%)	0.68
BMI (kg/m <sup>2</sup> )	25.7 ± 4.99	24.7 ± 3.69	0.62
Education (years)	15.8 ± 1.83	15 ± 2.1	0.34
BDI	4.8 ± 4.21	2.7 ± 2.76	0.18
BAI	3.4 ± 4.37	2.5 ± 3.64	0.60
NAART	19.2 ± 6.84	18.5 ± 9.09	0.85
TONI	41.2 ± 8.93	41 ± 8.28	0.96
Smoking (cig.)	0.6 ± 1.57	1.4 ± 3.59	0.54
Alcoholic drinks (avg. p.w.)	14.9 ± 11.77	16.4 ± 8.97	0.74
THC	0.3 ± 0.48	0.4 ± 0.5	0.77

<sup>a</sup> Values are expressed as mean ± standard deviation or n (%).

The exact mechanism by which this effect occurs in humans is unknown. However, recent work in the animal model suggests that compromised fatty-acid derived brain-gut communication plays a role. Nutrient infusion directly into the gut increases extracellular dopamine levels [3]. This response is compromised following a high fat diet, which concomitantly depletes intestinal levels of N-Acylethanolamines, a family of appetite-regulating fatty acid amides [12,13]. One such amide [14], oleoylethanolamide (OEA), which is synthesized in the intestine in response to dietary oleic acid [15], not only acts as a powerful satiety messenger by signaling via a nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα) [16], but also reverses diet-induced blunted striatal dopamine signaling [3]. Specifically, placing mice on a high fat diet decreases OEA levels in the intestine and blunts the rise in extracellular striatal dopamine normally observed in response to intragastric infusion of lipids. This blunting may then be reversed by intraperitoneal infusion of OEA. OEA infusion can also potentiate dopamine release in response to a low-fat intragastric infusion in lean animals on a low fat diet, an effect accompanied by a decrease in preference for high fatty foods demonstrating that the ability of OEA to influence striatal dopamine efflux is not restricted to the context of diet-induced dopamine adaptations [3]. Furthermore, intragastric injection of OEA in lean mice causes a decrease in preference for high fatty foods [17]. Whether similar effects can be observed in humans is unknown; however, plasma OEA levels are associated with brain responses to food images [18] and supplementation with the dietary supplement PhosphoLean™, which contains N-oleyl-phosphatidylethanolamine (NOPE), the precursor for OEA, increases compliance with weight loss programs [19,20], possibly indicating a beneficial effect of supplementation on self-control.

Similar to a high fat diet, prolonged heavy drinking of alcohol is associated with altered dopamine signaling [21] and impulsivity [11]. Alcohol abuse also clearly alters lipid metabolism [22] and liver function [23]. Similar to the effect of a high fat diet on OEA, alcohol intake releases OEA, and chronic ethanol administration decreased OEA levels in parallel with the onset of withdrawal symptoms [24]. Even more critically, OEA administration can block cue-induced reinstatement of alcohol-seeking behavior (the animal model for relapse). This suggests the intriguing possibility that OEA may be a novel therapeutic target

for alcohol use disorders and alcoholism. With this in mind we set out to perform a preliminary study to test if dietary supplementation with a fatty acid amide could reduce alcohol intake and impulsivity in a group of young adult heavy drinkers. Twenty-two participants underwent three weeks of dietary supplementation with PhosphoLean™ (30 mg N-oleyl-phosphatidylethanolamine (NOPE) + 20 mg epigallocatechin-3-gallate (EGCG) per capsule) or treatment with placebo. We predicted that impulsivity would decrease in the PhosphoLean™, but not placebo group, and that decreases in impulsivity would be associated with reduced alcohol intake. Given the animal data linking OEA administration with change in preference for fat [17] and to consider potential effects of OEA food choice, we also measured fat concentration preference.

## 2. Materials and methods

### 2.1. Participants

Twenty-two healthy human adults ranging in age from 21–45 years participated in the study. Participants had to meet NIAAA heavy drinking criteria [25] (5 or more standard drinks for men and 4 or more standard drinks for women on a drinking day) at least once per week for the prior 21 days, but they had to consume less than 40 drinks in total per week. Further criteria include right handedness, English speaking, and a body mass index (BMI expressed as kg/m<sup>2</sup>) within the range 18.5–35.

Participants were excluded if they had a past or current history of alcohol or drug abuse or dependence, or tested positive on any toxicology tests performed at each session (reported past or current use or positive test for Tetra Hydro Cannabinol (THC) was allowed), medical illness, psychiatric illness as defined by the DSM-IV criteria including eating disorders, medications that affect alertness, history of head trauma with loss of consciousness, diabetes, food allergy or ongoing pregnancy. Out of 29 recruited subjects seven did not complete the study: four because they were ineligible, two due to scheduling issues and one for not wanting to take the supplement.

Participants were recruited with flyers and online advertisements in the Yale University and the greater New Haven communities. Written informed consent was obtained and the protocol was approved by the Yale University Human Investigations Committee.

### 2.2. Supplement

PhosphoLean™ is a dietary supplement consisting of N-oleyl-phosphatidylethanolamine (NOPE) and epigallocatechin-3-gallate (EGCG). NOPE is extracted from soy phospholipids and EGCG is from standardized green tea extract. NOPE consists of OEA bound to phosphatidylethanolamine (PE). NOPE is a naturally occurring ethanolamine glycerol-phospholipid containing three fatty acid chains and is found in animal and vegetable foods that are part of the human diet. OEA activates PPARα found in the intestine tract through binding after oral administration [16]. EGCG polyphenols act synergistically with OEA via sympathetic activation of thermogenesis and increases fat oxidation [26]. Every capsule, supplied by CHEMI Nutra (White Bear Lake, MN),

**Table 2**  
Data and statistics of anthropometrics.

	PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 9) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,15] <sup>b</sup> 1.388	.285	–	–
Univariate								
BMI (kg/m <sup>2</sup> )	26.2 ± 5.91	26.14 ± 5.69	25.58 ± 5.22	26.09 ± 5.45	[1,17] 2.489	.133	.618	.113
BF (%)	28.19 ± 12.62	26.86 ± 12.63	24.9 ± 11.76	24.15 ± 12.09	1.154	.298	.125	.994
W/H ratio	0.91 ± 0.05	0.88 ± 0.08	0.88 ± 0.07	0.86 ± 0.09	1.444	.246	<b>.040</b>	.700

Bold font indicates statistically significant P-values of P < 0.05 and trends of P < 0.1.

<sup>a</sup> Values are expressed as mean ± standard deviation or n (%).

<sup>b</sup> Degrees of freedom [hypothesis, error].

**Table 3**  
Data and statistics for alcohol consumption of the TLFB.

	PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[6,14] <sup>b</sup> .719	.641	–	–
Univariate								
Total dr	49.31 ± 31.04	35.2 ± 26.12	49.07 ± 36.53	34 ± 16.06	[1,19].034	.857	.112	.069
Drinking days (n)	10 ± 5.93	8.27 ± 4.8	10.18 ± 3.66	8.45 ± 3.93	.049	.827	.209	.123
Average dr/drdy	4.75 ± 2.72	4.33 ± 2.35	5.01 ± 3.26	3.87 ± 1.98	.617	.442	.481	.083
Heavy drdy	3.36 ± 2.5	2.73 ± 2.2	3.36 ± 2.54	2.64 ± 1.75	.025	.875	.293	.207
Max dr/dy	12.34 ± 11.3	7.63 ± 3.97	13.34 ± 16.13	10.61 ± 6.36	.136	.716	.249	.513

<sup>a</sup> Values are expressed as mean ± standard deviation.<sup>b</sup> Degrees of freedom [hypothesis, error].

contains 30 mg of NOPE and 20 mg of EGCG. PhosphoLean™ 40P is a dietary ingredient under the Dietary Supplement Health and Education Act (DSHEA) regulations of the US FDA (1994).

Participants were assigned in a double-blind manner to dietary supplementation with PhosphoLean™ or placebo. We instructed participants to take 6 capsules a day for three weeks (21 days); two capsules consumed one hour before lunch, two capsules one hour prior to dinner, and two capsules two hours after dinner. The dosage was chosen based on previous reports in the literature [19,20] and recommendation from the supplier. We chose this schedule of delivery to maximize the effect of the supplement in the evening hours when most alcohol is consumed. The placebo was identical in appearance to the PhosphoLean™ capsules, but contained 100 mg of rice flour per capsule. Text message reminders were sent weekly to increase adherence with taking the dietary supplement or placebo, together with a weekly phone call to ask about adherence and experience of any side effects. Subjects were not explicitly instructed to change their alcohol consumption and were told that apart from taking their supplement they could continue their regular routine.

### 2.3. Study design

After phone screening, participants were invited to participate in three sessions; an intake session, followed by a pre-treatment session on a separate day and a post-treatment session after 3 weeks of supplementation.

To exclude psychiatric conditions and control for post-hoc group differences, participants were interviewed, filled out questionnaires, and completed intelligence tests, during the intake session. To exclude psychiatric conditions and drug or alcohol abuse or dependence the Mini International Neuropsychiatric Interview (MINI) [27], the Beck Anxiety Inventory (BAI) [28] and the Beck Depression Inventory (BDI) [29] were given. Smoking, marijuana, and alcohol use in the past three weeks was measured with the timeline follow back (TLFB) [30] to ensure eligibility. Verbal intelligence was measured with the North American Adult Reading test (NAART) [31] and non-verbal intelligence with the Test of Non-verbal intelligence (TONI) [32]. Following the intake session, eligible

participants were assigned to treatment conditions and participants scheduled for a pre- and post-treatment session. Assignment to treatment condition was performed by a simple coin toss for the first 10 participants and subsequent participants were allocated to treatment groups to minimize differences between the two groups on demographics and anthropometrics (age, gender, BMI, education level, depression, anxiety, verbal and non-verbal intelligence, smoking, alcohol and THC use at intake).

During both the pre- and post-treatment sessions, participants arrived at the lab between 8 AM and 2 PM for a 12-hour fasting blood draw (water was allowed). Participants then underwent a breath alcohol test (using the Alcohawk Elite Breathalyzer), urine toxicology tests (with the Integrated E-Z Split Key Cup II) for THC, benzodiazepines, cocaine, (meth) amphetamines and opiates, and if applicable, a urine pregnancy screening. Anthropometric measures including BMI, waist-hip ratio and relative body fat, measured with a BodPod body composition tracking system (Cosmed), which is an air displacement plethysmograph, were also obtained at each session. Finally, participants filled out questionnaires, completed a TLFB interview, three behavioral tasks and a fat/sweet concentration preference task. We provide details for each of these questionnaires and tasks below. The study was approved by the Yale Medical School Institutional Review Board (Clinical trials registration number: NCT01902069).

### 2.4. Outcome measures

The effect of PhosphoLean™ on alcohol consumption as assessed by the TLFB interview and impulsivity were considered the main outcome measures. Secondary outcome measures were food intake, eating behavior, physical activity, anxiety, depressive symptoms, response inhibition, sensitivity to negative outcome learning, and fat concentration preference.

#### 2.4.1. TLFB interview

To have an accurate indication of the quantity and frequency of alcohol consumption during the prior 21 days the TLFB was administered by trained interviewers [30]. Participants were interviewed about their

**Table 4**  
Data and statistics of the BIS-11.

	PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,17] <sup>b</sup> .436	.730	–	–
Univariate								
Attentional	17.09 ± 3.14	17.82 ± 4.49	17.45 ± 3.01	17.64 ± 4.13	[1,19].282	.602	.311	.776
Motor	22.45 ± 4.32	22.64 ± 4.57	23.45 ± 4.87	22.45 ± 3.45	1.266	.275	.774	.208
Non-planning	23.36 ± 2.91	23.91 ± 3.11	23.09 ± 4.48	23.45 ± 4.99	.003	.953	.375	.419
Total	62.91 ± 8.06	64.36 ± 8.94	64 ± 9.91	63.55 ± 10.5	1.062	.316	.274	.741

<sup>a</sup> Values are expressed as mean ± standard deviation.<sup>b</sup> Degrees of freedom [hypothesis, error].

**Table 5**  
Data and statistics of the TFEQ.

	PhosphoLean (n = 10) <sup>a</sup>		Placebo (n = 10) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,15] <sup>b</sup>	.292	–	–
Univariate								
Restraint	7.73 ± 5.5	7 ± 6.32	8.6 ± 3.92	9.36 ± 5.95	[1,17]	.855	.395	.660
Disinhibition	6.09 ± 4.11	4.4 ± 1.58	5.3 ± 4.27	4.55 ± 4.25	.032	.859	.312	.211
Hunger	6.36 ± 3.11	5.6 ± 3.69	5.2 ± 2.74	5.36 ± 3.14	.093	.765	.516	.821

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].

alcohol consumption for each day using a calendar and key dates as memory prompts. Samples of different cups and glasses in various sizes and shapes were provided to facilitate accurate reporting. Additionally, brand names were noted and percent alcohol verified. The TLFb has demonstrated good psychometric properties in numerous studies [33].

#### 2.4.2. Questionnaires

To measure impulsivity, we asked participants to fill out the Barratt Impulsiveness Scale Version 11 (BIS-11) [34], which consists of motor (impudent action), attentional (impatience with complexity and rapid shifts) and non-planning (lack of future orientation) impulsivity subscales. Cognitive control of eating (conscious considerations about food intake), ability to inhibit eating (uncontrolled food intake) and feelings about hunger (emotional influence on food intake) were measured with the Three Factor Eating Questionnaire (TFEQ) [35]. We estimated physical activity using the International Physical Activity Questionnaire (IPAQ) [36].

To evaluate overall fat intake participants completed the Dietary Fat and Free Sugar Questionnaire (DFS) [37], which collects information about the frequency of food eaten over the past 12 months. The DFS has four subscales to estimate consumption of saturated fats and free sugars: total score, saturated fat, free sugar intake and fat-sugar. Finally, to assess depression and anxiety participants filled out the BDI and the BAI.

#### 2.4.3. Behavioral tasks

We used the Go/No-Go task [38] to examine selective attention and response control. During the task the participant was instructed to press a response key (spacebar) as quickly as possible to a Go stimulus (X) and withhold their response to a No-Go stimulus (K), which appeared in different frequencies (87% X and 13% K) on a black computer screen (250 milliseconds (ms) display, 1000 ms inter trial interval). The appearance of Go and No-Go stimuli was pseudorandomized with intervals of 10–15 s between No-Go stimuli. The task consisted of two blocks with 246 trials each lasting 7 min 21 s, producing a total of 492 total trials per participant. A break of approximately one min was provided between the blocks.

To assess the ability to learn from positive and negative outcomes we used The Probabilistic-Feedback Reward Task (PFRT) [39]. On each trial, the participant is presented with two unfamiliar symbols, asked to choose one symbol, and then receives feedback (“correct” or “incorrect”). The symbols are presented in three pairs: AB, CD and EF, counterbalanced across participants with a unique set of symbols used

for each session. The probability of receiving “correct” feedback for each symbol pair is 80/20, 70/30, and 60/40%, respectively. The task begins with a training period of variable duration during which the participant receives feedback and must learn which stimulus is associated with positive feedback and which is associated with negative feedback. Pairs are presented in blocks of 60 choices until the participant reaches a threshold level of performance. After criterion is reached the participant continues with the same task, but the choices are presented in new pairs (AC, AD, AE, AF, BC, BD, BE, BF) and no feedback is given. The ability to learn from positive feedback is determined by examining the number of times the participant chooses A, and the ability to learn from negative feedback was determined by counting the number of times that they successfully avoided choosing B. The ability to learn from positive outcomes has been postulated to be related to D1 receptor signaling, whereas ability to avoid negative outcomes has been postulated to be related D2 receptor signaling [40].

The Experiential Discounting Task (EDT) [41] measures delay discounting. The task consists of four blocks, each with a minimum of 16 choices between a delayed and immediate outcome. In each block the delayed option has a standard value (\$0.30), is probabilistic (35% change of receiving), and delayed by a consistent interval (0, 15, 30, or 60 s). The immediate option is an adjusting amount of money (starting at \$0.20, range of \$0.10 and \$0.25) that is immediate and certain (100% chance of receiving). On each trial the participant chooses between the delayed and immediate option. They then “cash in” by clicking a button on a coin dispenser. If the participant chooses the delayed amount, the immediate amount for the next choice is increased by \$0.05. If the participant chooses the immediate amount, the immediate amount for the next choice is decreased by \$0.05. If a participant selects the same choice four consecutive times, they are forced to select the other choice (i.e., only one outcome button was presented). Between blocks there is an inter-block interval to ensure a block could not be ended more quickly by any specific choice sequence. The total amount of money made after completing the whole task was added to the check amount for the participant payment.

#### 2.4.4. Fat concentration preference assessment

To assess fat and sweet concentration preference participants rated puddings and Jell-O on a variety of attributes. The General Labeled Magnitude Scale (gLMS) [42] was used to assess intensity perception. It is a vertical line with quasi-logarithmic spaced labels that start at the bottom with ‘barely detectable’ to ‘strongest imaginable’ at the top. The Labeled Hedonic Scale (LHS) was used to assess liking [43]. It is similar to the gLMS, but the end labels are ‘most imaginable dislike’ to ‘most

**Table 6**  
Data and statistics of the IPAQ.

	PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
MET-MINUTES/WK	8066 ± 4487	9411 ± 6464	19,332 ± 30,621	14,548 ± 18,671	[1,19] <sup>b</sup>	2.824	.572	.087

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].



**Table 7**  
Data and statistics of the DFS.<sup>a</sup>

	PhosphoLean (n = 9) <sup>a</sup>		Placebo (n = 10) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,14] <sup>b</sup> .571	.643	–	–
Univariate								
Total	55.33 ± 9.67	51.64 ± 9.89	57.2 ± 8.84	53 ± 5.4	[1,16].751	.339	<b>.028</b>	.224
Satfat	29.33 ± 5.61	27.45 ± 7.24	29.9 ± 5.04	26.36 ± 3.59	.188	.670	<b>.034</b>	.090
Sugar	11.22 ± 4.06	10.45 ± 2.11	11 ± 3.09	10.91 ± 1.7	.082	.778	.855	.809
Fat-sugar	14.78 ± 3.42	13.73 ± 2.97	16.3 ± 3.16	15.73 ± 3.13	1.690	.212	.890	.843

Bold font indicates statistically significant P-values of  $P < 0.05$  and trends of  $P < 0.1$ .

DFS, dietary fat and free sugar question; satfat, saturated fat.

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].

imaginable like', with the label 'neutral' in the middle. Visual Analogue Scales (VAS) were used to assess hunger, fullness, thirst, oiliness, fattiness, creaminess and wanting. The VAS is a horizontal line anchored by 'not at all' at one end and 'extremely' at the other [44]. The puddings (Jell-O, Kraft Foods with milk Guida's Dairy) were made with four different concentrations of fat: 0%, 3.1%, 6.9%, and 15.6% (with constant sugar content (w/w)) [45]. The Jell-O's (flavored with Kool-Aid and deionized water) were made with four different concentrations of sucrose: 0, 0.1, 0.56, and 1 M. Participants chose their preferred flavor prior to the start of the task (vanilla and chocolate pudding and orange or strawberry Jell-O).

The task started with the participant rating how hungry, full, and thirsty they felt. Then a stimulus was presented on a tasting spoon ( $\pm 1.5$  mL) while the participant was blindfolded (to prevent differences in the color of the puddings from influencing ratings). After tasting and swallowing each stimulus, the participant removed the blindfold, rated the intensity, sweetness, liking, oiliness, fattiness, creaminess and wanting, then rinsed with deionized water and waited for 30 s before putting on the blindfold and receiving the next stimulus. Stimuli were delivered in blocks (pudding or Jello-O) and each stimulus was repeated three times in a randomized order.

## 2.5. Data analysis

All statistical analyses were done using IBM SPSS statistics 21. To evaluate group difference on intake measures, we used an independent sample t-test. To evaluate how supplementation with PhosphoLean<sup>TM</sup> affected outcome measures, we conducted a repeated measures MANOVA for each of the questionnaires and tasks, with group (PhosphoLean<sup>TM</sup> and placebo) as a between-participants factor, and time (pre and post) as a within-subjects factor, gender as a covariate, and subscales or sub measures as independent measures. We inspected the multivariate and univariate interaction effect of group and time. We report post-hoc pairwise comparisons of time within each group for significant and trending P-values. To investigate whether change from pre-supplementation to post-supplementation of any significant secondary outcome measures correlated with the primary outcome measure of alcohol consumption, correlation analyses were performed with non-

parametric Spearman's coefficient to increase sensitivity due to low number of observations. We considered P-values  $< 0.05$  as statistically significant and report P-values  $< 0.1$  as a trend. We repeated all analyses with BMI as a covariate and the results were unchanged.

### 2.5.1. TLFB interview

The answers on the TLFB were converted to standard alcoholic drinks per day. We then calculated: total drinks in the past 21 days (total dr), number of days drinking (drdy), the average amount of standard drinks per drinking day (dr/drdy), the maximum number of drinks per day (max dr/dy), and number of heavy drinking days per week ( $m \geq 5$  and  $f \geq 4$  drinks per day, heavy drdy). To evaluate how supplementation with PhosphoLean<sup>TM</sup> affected alcohol consumption, we conducted a repeated measures ANOVA, with group (PhosphoLean and placebo) as a between-subject factor, and time (pre and post) as a within-subject factor, gender as a covariate, and total dr, drdy, dr/drdy, max dr/dy, and heavy drdy as independent measures.

### 2.5.2. Questionnaires

BIS11, TFEQ and DFS were recoded and scored as instructed in user manuals. From the IPAQ, the metabolic equivalent minutes per week (MET-minutes/WK) was calculated by multiplying metabolic intensity with the minutes for each activity over the last week. For the BDI and BAI scores were calculated by a simple sum of all answers.

### 2.5.3. Behavioral tasks

In every trial of the Go/No-Go task, there are four possible stimulus/response combinations as an outcome; a response to a Go stimulus is classified a "hit", a response to a No-Go stimulus is a "false alarm", not responding to a Go stimulus is a "miss", and no response to No-Go stimulus is a "correct rejection". Proportion of hits (pH) and false alarms (pFA) were included in our analysis and proportion of misses and correct rejections were omitted since these are perfectly correlated to hit and false alarm rates. Besides these two measures, the reaction time of the hits (rtH) and the reaction time of the false alarms (rtFA) was registered.  $D'$  (proportion of hits–proportion false alarms) was calculated to show the effectiveness of individual decision making. To evaluate how supplementation with PhosphoLean<sup>TM</sup> affected response inhibitions,

**Table 8**  
Data and statistics of the BDI, BAI.

	PhosphoLean (n = 10) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[2,17] <sup>b</sup> 3.430	.056	–	–
Univariate								
BDI	5.18 ± 4	6.36 ± 5.9	3.91 ± 4.76	2.91 ± 3.48	[1,18] 4.501	<b>.048</b>	.084	.255
BAI	3.64 ± 2.94	3.2 ± 3.22	3.18 ± 4.49	3.55 ± 5.15	.131	.721	.826	.772

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].

**Table 9**  
Data and statistics for response inhibition in Go/No-Go.

	PhosphoLean (n = 10) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre	Post	Pre	Post	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[5,14] <sup>b</sup> 1.744	.189	–	–
Univariate								
pH	0.98 ± 0.03	0.99 ± 0.02	0.97 ± 0.07	0.98 ± 0.05	[1,18] .126	.726	.891	.515
pFA	0.4 ± 0.2	0.28 ± 0.09	0.39 ± 0.17	0.41 ± 0.19	4.028	<b>.060</b>	<b>.034</b>	.611
rtH	356.83 ± 39.62	364.5 ± 31.18	359.18 ± 54.14	363.05 ± 55.58	.085	.774	.926	.713
rtFA	335.36 ± 62.51	330.44 ± 17.43	310.41 ± 34.79	339.44 ± 43.47	5.005	<b>.038</b>	.267	<b>.054</b>
d'	2.54 ± 1.09	3.09 ± 0.64	2.75 ± 1.12	2.7 ± 0.88	1.105	.307	.206	.877

Bold font indicates statistically significant P-values of  $P < 0.05$  and trends of  $P < 0.1$ .

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].

we conducted a repeated measures ANOVA, with group (PhosphoLean™ and placebo) as a between-subject factor, and time (pre and post) as a within-subject factor, gender as a covariate, and pH, pFA, rtH, rtFA and d' as independent measures.

Outcome measures on the PFRT were the proportion of times the participant chose A, avoided B, and the number of blocks needed to perform at criterion in the training phase.

For the EDT we calculated the indifference point; the point at which the participant evaluates the two choices as equally reinforcing. A titration procedure was designed to find a stable point of indifference between the delayed and immediate amounts. Stability was defined as the time that three out of the previous six free choices were made for the immediate option. We calculated the area under the discount curve (AUC) with the formula  $V = A / (1 + kD)$ , where V represents the value of the delayed reinforcer, A is the amount of the reinforcer and D the length of delay to its delivery, k indicates the steepness of the discount curve.

#### 2.5.4. Fat concentration preference assessment

Ratings from the fat and sweet concentration preference test were averaged across the three presentations of the same stimulus concentration within each participant, and then entered into a repeated measures MANOVA with group (PhosphoLean™ and placebo) as a between-subject factor and time (pre and post) and concentration (1–4) as within-subject factors, gender as a covariate and rating scales for puddings and Jell-O's as independent measures. We inspected the

multivariate and univariate interaction effect of group and time, as well as the interaction effect of group, time and concentration.

We also coded variables for change from pre to post-supplementation in most preferred concentration for puddings and Jell-Os by using: 1) change in concentration steps (negative values for decreased preferred concentration and positive values for increased preferred concentration), 2) change in absolute concentration steps, and 3) a dummy variable with a value of 1 for a change in concentration and 0 for no change in concentration. To test for differences between treatment groups, these variables were each tested with a nonparametric independent-samples Mann–Whitney U test.

### 3. Results

#### 3.1. Side effects

One participant reported feeling stomach discomfort after taking the supplement shortly before a meal on one occasion but remained in the study.

#### 3.2. Demographics & anthropometrics

As displayed in Table 1, the groups did not differ in age, gender, BMI, education level, depression, anxiety, verbal and non-verbal intelligence, smoking, alcohol and THC use at intake. Treatment had no effect on anthropometrics (Table 2).

#### 3.3. TLFB interview

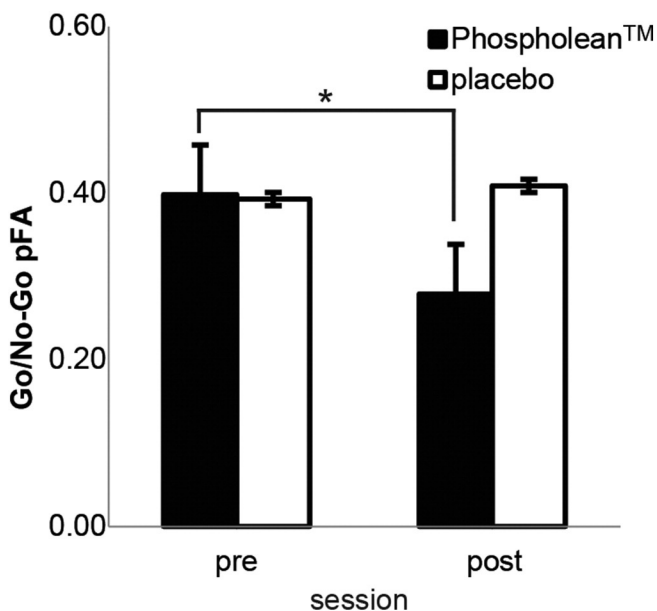
There was no effect of treatment on any of the alcohol intake measures (Table 3).

#### 3.4. Questionnaires

No significant effect of treatment was found for the BIS-11 (Table 4), TFEQ (Table 5), IPAQ (Table 6), DFS (Table 7) or BAI (Table 8). However, we observed a group by time interaction on the BDI with symptoms of depression tending to increase in the PhosphoLean™ group from pre to post-supplementation (Table 8).

#### 3.5. Behavioral tasks

We observed a trend for an interaction between treatment group and time on the Go/No-Go task, such that supplementation with PhosphoLean™, but not placebo, decreased the proportion of false alarms (Table 9 and Fig. 1) from pre to post-supplementation. We also observed a significant interaction between time and treatment group on the response times for false alarms, which was driven primarily by response times decreasing in the placebo group from pre to post-supplementation (Table 9). No effect of treatment was observed on the PFRT (Table 10) or EDT (Table 11).



**Fig. 1.** Average proportion false alarms (+/– standard error of the mean) on the Go/No-Go Task for the PhosphoLean™ group (solid bars) versus placebo group (open bars) in pre versus post-test. \*Pairwise comparison  $p < 0.05$ .

**Table 10**  
Data and statistics for the PFRT.

	PhosphoLean (n = 10) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Pairwise comparison p	
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo
Multivariate	–	–	–	–	[3,16] <sup>b</sup>	.423	–	–
Univariate								
Choose A	61.36 ± 24.5	59.1 ± 21.36	71.03 ± 22.06	68.75 ± 21.83	[1,18]	.008	.928	.848
Avoid B	61.37 ± 27.51	61.37 ± 29.56	57.95 ± 24.54	64.77 ± 28.4	.352	.560	.809	.278
Blocks	3.8 ± 2.2	4.18 ± 2.09	2.73 ± 2.05	3.91 ± 1.87	.731	.404	.824	.157

<sup>a</sup> Values are expressed as mean ± standard deviation.<sup>b</sup> Degrees of freedom [hypothesis, error].

### 3.6. Fat concentration preference assessment

Treatment had no effect on fat concentration preference (Tables 12 and 13). However, we did observe a trend for an interaction between treatment group and time on sweetness ratings for both puddings and Jell-O's, such that supplementation with PhosphoLean™, but not placebo decreased sweetness intensity ratings (Table 12). Treatment had no effect on any of the other variables in the fat concentration preference assessment.

### 3.7. Relation between alcohol intake and Go/No-Go task

We observed a relation between change in alcohol intake from pre to post-supplementation and change in performance on the Go/No-Go task from pre to post test when considering the entire sample (control and PhosphoLean) (Fig. 2). Specifically, the change of proportion of false alarms was positively associated with change in maximum drinks per drinking day, and change in *d'* was negatively associated with change in total drinks consumed as well as change in number of heavy drinking days. These observations for the Go/No-Go task indicate that consumption of fewer drinks is associated with greater sensitivity (false alarms relative to hits), indicative of less impulsivity.

## 4. Discussion

The primary goal of this study was to test the prediction that increasing gut fatty acid amide levels by three weeks of dietary supplementation with PhosphoLean™ can reduce impulsivity and alcohol intake in heavy drinkers. Our findings provide partial support for this possibility. While we did not observe a main effect of the supplement on self-reported alcohol intake, we did find that supplementation with PhosphoLean, but not placebo, led to improvements on a task of motor impulsivity. Reduced motor impulsivity was, in turn, related to reductions in alcohol intake. Collectively, the results provide preliminary support for a novel mechanism to reduce impulsivity that may translate into reduced alcohol consumption in heavy drinkers.

Alcohol use disorders and alcoholism are associated with impulsive behavior and compromised dopamine signaling [11,21]. Recent data from rodents demonstrates that the compromised dopamine signaling observed following a high fat diet is associated with the depletion of a family of appetite-regulating fatty acid amides from the gut, which when replenished rescues dopamine signaling and shifts preferences towards lower fat foods [3]. With respect to alcohol, ethanol

administration increases OEA levels in variety of tissues including the nucleus accumbens [24]. Following chronic ethanol administration OEA levels then drop in parallel with the onset of withdrawal behaviors. Resembling effects with the high fat diet acute OEA administration can then reduce withdrawal symptoms and block cue-induced reinstatement of alcohol seeking behavior – the animal model of relapse. This raises the possibility that OEA may have therapeutic effects for alcohol use disorders and alcoholism.

Our data provide preliminary support for this possibility. After only three weeks of supplementation with PhosphoLean, which contains the precursor to OEA and is converted to OEA in the gut [16], we observed an improvement on a standard behavioral measure of impulsivity in heavy drinking young adults. Specifically, false alarm responses on the Go/No-Go task decreased significantly in the PhosphoLean™, but not the placebo control group. Whether this improvement reflects a rescuing of gut-brain communication is unknown. However, false alarm rate on this same task has been linked to the dorsal striatal dopamine adaptation observed in obesity [8], suggesting that improved performance might have resulted from rescuing dorsal striatal dopamine signaling compromised by heavy drinking. Future studies are warranted to test this possibility.

We also found that reductions in motor impulsivity correlated with reductions in maximal drinks consumed per day. Although this occurred irrespective of group it supports the possibility that supplementation may influence core functions (i.e. motor impulsivity), which in turn relate to positive behavioral change. As such, studies assessing whether longer supplementation in a larger sample might translate into a reduction of adverse consequences of decision-making are called for. For example, participants on the dietary supplement may make fewer bad decisions, such as drinking and driving. It may also be that the effects of the supplement would have been more pronounced in heavy drinkers who are looking to reduce drinking and when looking at the effects of the supplement on maintenance of abstinence (for example, with reduced impulsivity, participants may be less likely to relapse to drinking).

Contrary to our prediction, supplementation with PhosphoLean™ did not change self-reported impulsivity (BIS-11). A possible explanation for the discrepant findings in the behavioral task and self-report measure may be related to the length of our trial. The BIS-11 measures trait impulsivity [34], with questions designed to have the respondent reflect upon their typical behaviors in a number of situations. It may well be that three weeks is too short a period of time for individuals to change self-perception. An alternative explanation is that the BIS-11 and Go/No-Go measure different aspects of impulsivity, which are

**Table 11**  
Data and statistics for the EDT.

	PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 9) <sup>a</sup>		Time × group interaction		Pairwise comparison p		
	Pre-test	Post-test	Pre-test	Post-test	F	p	PhosphoLean	Placebo	
AUC	1.22 ± 2.5	0.45 ± 0.19	0.52 ± 0.15	0.55 ± 0.14	[1,17] <sup>b</sup>	1.205	.288	.155	.892

<sup>a</sup> Values are expressed as mean ± standard deviation.<sup>b</sup> Degrees of freedom [hypothesis, error].

**Table 12**  
Data and statistics for the fat preference concentration assessment.

		PhosphoLean (n = 11) <sup>a</sup>		Placebo (n = 11) <sup>a</sup>		Time × group interaction		Time × group × concentration interaction		Pairwise comparison p			
		Pre-test	Post-test	Pre-test	Post-test	F	p	F	p	PhosphoLean	Placebo		
Multivariate						[16,4] <sup>b</sup>	1.107	.515	[48,132]	.741	.882	–	–
Univariate													
LHS pudding	0%	12.74 ± 6.86	11.28 ± 6.01	6.36 ± 6.86	4.86 ± 6.01	[1,19]	.000	.987	[3,57]	1.130	.344	.883	.864
	3.1%	20.46 ± 6.35	17.93 ± 5.87	10.81 ± 6.35	11.05 ± 5.87								
	6.9%	22.02 ± 6.26	25.98 ± 6.10	16.28 ± 6.26	12.02 ± 6.10								
	15.6%	25.62 ± 6.66	23.17 ± 6.38	11.51 ± 6.66	14.17 ± 6.38								
LMS pudding	0%	19.70 ± 3.21	14.28 ± 2.91	25.92 ± 3.21	22.64 ± 2.91	1.452	.243	.249			.862	.126	.914
	3.1%	19.90 ± 3.73	14.22 ± 2.77	22.07 ± 3.73	22.36 ± 2.77								
	6.9%	23.27 ± 3.47	19.80 ± 3.05	21.81 ± 3.47	23.21 ± 3.05								
	15.6%	23.25 ± 3.73	20.96 ± 3.24	20.86 ± 3.73	23.60 ± 3.24								
Saltiness pudding	0%	1.75 ± 1.95	2.48 ± 3.42	8.51 ± 1.95	10.43 ± 3.42	.081	.779	.112			.953	.991	.700
	3.1%	2.28 ± 1.87	1.49 ± 2.98	7.20 ± 1.87	7.83 ± 2.98								
	6.9%	1.10 ± 1.68	0.80 ± 1.77	7.22 ± 1.68	7.30 ± 1.77								
	15.6%	1.09 ± 2.57	1.38 ± 2.89	10.98 ± 2.57	10.97 ± 2.89								
Sweetness pudding	0%	18.31 ± 3.15	13.20 ± 3.50	20.18 ± 3.15	21.39 ± 3.50	3.160	.091	.596			.620	.052	.661
	3.1%	22.30 ± 3.22	15.16 ± 3.43	21.02 ± 3.22	23.58 ± 3.43								
	6.9%	25.03 ± 3.12	18.96 ± 3.20	23.76 ± 3.12	22.30 ± 3.20								
	15.6%	23.88 ± 3.61	20.33 ± 4.12	19.59 ± 3.61	21.98 ± 4.12								
Creaminess pudding	0%	40.91 ± 4.78	40.10 ± 5.89	46.85 ± 4.78	38.41 ± 5.89	.173	.682	1.434			.242	.227	.082
	3.1%	50.05 ± 5.32	42.86 ± 5.98	55.34 ± 5.32	47.66 ± 5.98								
	6.9%	52.58 ± 4.63	45.43 ± 5.92	54.37 ± 4.63	49.80 ± 5.92								
	15.6%	53.56 ± 5.63	48.16 ± 6.34	60.11 ± 5.63	50.55 ± 6.34								
Fattiness pudding	0%	28.49 ± 5.88	22.86 ± 6.21	35.83 ± 5.88	33.93 ± 6.21	.084	.775	.092			.964	.329	.561
	3.1%	34.78 ± 7.19	26.96 ± 6.58	44.17 ± 7.19	38.61 ± 6.58								
	6.9%	33.84 ± 6.20	30.54 ± 6.69	39.72 ± 6.20	38.55 ± 6.69								
	15.6%	35.89 ± 6.78	31.19 ± 6.95	48.18 ± 6.78	44.15 ± 6.95								
Oiliness pudding	0%	4.51 ± 2.98	3.95 ± 3.51	31.26 ± 2.98	24.53 ± 3.51	1.466	.241	2.027			.120	.958	.093
	3.1%	3.27 ± 3.15	4.46 ± 3.98	31.28 ± 3.15	28.26 ± 3.98								
	6.9%	5.50 ± 3.14	4.83 ± 3.95	27.41 ± 3.14	29.01 ± 3.95								
	15.6%	5.20 ± 3.68	4.81 ± 3.64	34.37 ± 3.68	28.49 ± 3.64								
Wanting pudding	0%	33.53 ± 7.27	34.49 ± 5.85	24.57 ± 7.27	20.01 ± 5.85	.598	.449	.684			.566	.420	.789
	3.1%	37.48 ± 7.85	40.63 ± 6.32	30.23 ± 7.85	29.45 ± 6.32								
	6.9%	37.69 ± 8.23	46.51 ± 6.33	35.59 ± 8.23	32.08 ± 6.33								
	15.6%	42.39 ± 8.50	47.90 ± 7.80	25.21 ± 8.50	27.96 ± 7.80								
LHS Jell-O	0 M	−39.73 ± 5.79	−42.04 ± 7.91	−36.82 ± 5.79	−33.31 ± 7.91	.006	.938	.407			.748	.426	.491
	0.1 M	−18.41 ± 5.34	−17.38 ± 5.75	−15.77 ± 5.34	−17.05 ± 5.75								
	0.56 M	16.31 ± 4.39	14.63 ± 6.54	11.68 ± 4.39	6.41 ± 6.54								
	1 M	14.45 ± 7.10	9.04 ± 7.08	10.29 ± 7.10	6.11 ± 7.08								
LMS Jell-O	0 M	32.29 ± 4.46	29.77 ± 5.05	29.37 ± 4.46	31.04 ± 5.05	1.472	.240	.708			.551	.491	.322
	0.1 M	19.76 ± 3.88	16.70 ± 2.89	17.22 ± 3.88	22.97 ± 2.89								
	0.56 M	24.45 ± 3.34	24.47 ± 2.88	20.41 ± 3.34	22.41 ± 2.88								
	1 M	34.65 ± 3.92	32.53 ± 4.08	26.06 ± 3.92	27.80 ± 4.08								
Saltiness Jell-O	0 M	14.13 ± 4.71	9.63 ± 6.26	14.76 ± 4.71	14.94 ± 6.26	.271	.608	.262			.853	.850	.591
	0.1 M	5.30 ± 2.94	6.11 ± 3.92	9.96 ± 2.94	10.34 ± 3.92								
	0.56 M	0.21 ± 0.70	0.95 ± 2.55	2.83 ± 0.70	5.82 ± 2.55								
	1 M	0.85 ± 0.84	1.52 ± 2.35	2.79 ± 0.84	5.73 ± 2.35								
Sweetness Jell-O	0 M	2.02 ± 1.28	1.52 ± 1.41	4.57 ± 1.28	6.23 ± 1.41	3.745	.068	.198			.898	.082	.378
	0.1 M	3.15 ± 1.01	3.82 ± 2.12	6.82 ± 1.01	10.94 ± 2.12								
	0.56 M	26.89 ± 3.64	21.43 ± 2.73	22.31 ± 3.64	22.77 ± 2.73								
	1 M	35.54 ± 3.68	30.62 ± 5.57	32.63 ± 3.68	31.40 ± 5.57								
Creaminess Jell-O	0 M	1.66 ± 2.61	1.59 ± 2.66	8.73 ± 2.61	9.38 ± 2.66	.906	.353	1.174			.328	.980	.201
	0.1 M	2.11 ± 2.52	1.53 ± 3.01	7.04 ± 2.52	9.58 ± 3.01								
	0.56 M	3.25 ± 3.14	2.22 ± 3.72	8.65 ± 3.14	14.35 ± 3.72								
	1 M	3.83 ± 4.13	5.27 ± 4.48	12.32 ± 4.13	16.16 ± 4.48								
Fattiness Jell-O	0 M	4.27 ± 4.87	3.78 ± 4.72	14.65 ± 4.87	12.03 ± 4.72	.002	.965	.968			.414	.309	.281
	0.1 M	5.41 ± 4.73	4.06 ± 4.51	14.68 ± 4.73	11.27 ± 4.51								
	0.56 M	8.04 ± 5.48	5.47 ± 5.16	16.66 ± 5.48	13.98 ± 5.16								
	1 M	11.24 ± 6.15	6.11 ± 5.23	16.71 ± 6.15	15.30 ± 5.23								
Oiliness Jell-O	0 M	3.21 ± 3.55	1.75 ± 5.17	14.29 ± 3.55	21.38 ± 5.17	3.045	.097	.606			.614	.821	.037
	0.1 M	3.30 ± 3.45	2.70 ± 4.78	11.33 ± 3.45	19.64 ± 4.78								
	0.56 M	2.75 ± 2.96	2.80 ± 4.38	11.06 ± 2.96	17.49 ± 4.38								
	1 M	2.93 ± 3.22	1.74 ± 4.67	10.21 ± 3.22	19.72 ± 4.67								
Wanting Jell-O	0 M	4.70 ± 2.31	7.12 ± 2.43	5.82 ± 2.31	3.43 ± 2.43	3.511	.076	.383			.766	.346	.107
	0.1 M	11.61 ± 3.70	14.65 ± 4.15	9.82 ± 3.70	10.79 ± 4.15								
	0.56 M	30.04 ± 7.12	35.16 ± 7.09	26.13 ± 7.12	22.19 ± 7.09								
	1 M	37.75 ± 8.66	35.87 ± 7.06	26.83 ± 8.66	16.97 ± 7.06								

<sup>a</sup> Values are expressed as mean ± standard deviation.

<sup>b</sup> Degrees of freedom [hypothesis, error].



**Table 13**

Data and statistics for non-parametric analyses of most liked fat and sweet concentration.

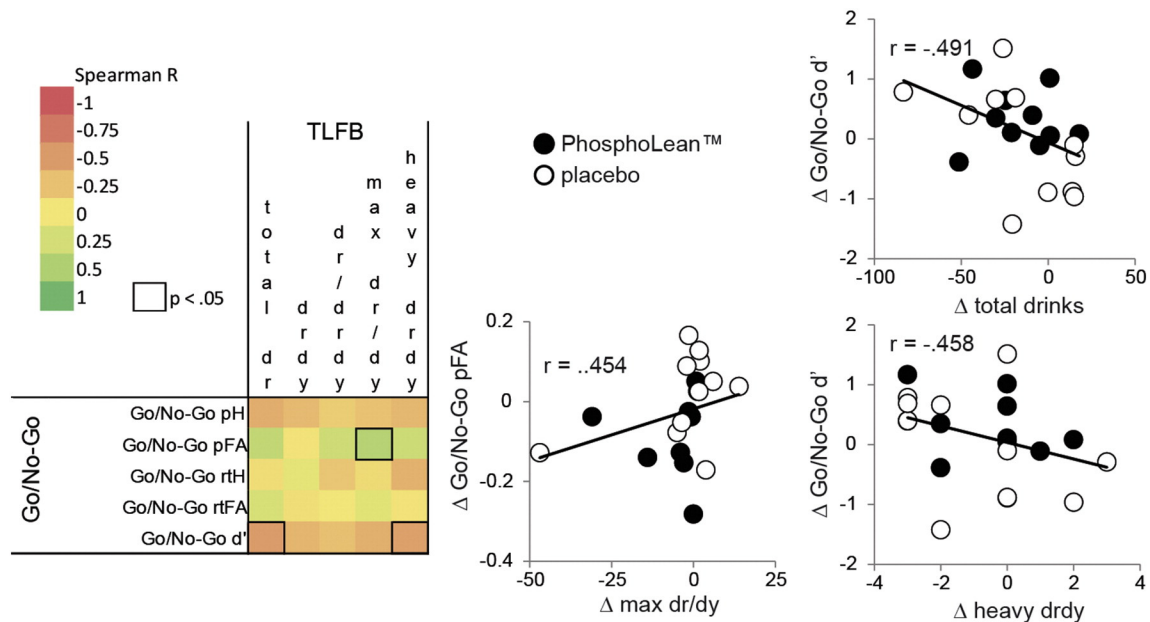
	Conc	PhosphoLean (n = 11)		Placebo (n = 11)		Variable	Mann-Whitney U p
		Pre-test	Post-test	Pre-test	Post-test	Pre-test pudding	
Most liked pudding	0%	2	2	0	2	Post-test pudding	.332
	3.1%	3	2	2	2	Pre-test Jell-O	.300
	6.9%	2	4	4	1	Post-test Jell-O	.519
	15.6%	4	3	5	6	Post-test Jell-O	.116
						Δ conc steps pudding	.699
Most liked Jell-O	0 M	0	0	0	0	Δ conc steps Jell-O	.797
	0.1 M	0	0	0	1	Δ  conc steps pudding	.652
	0.56 M	6	4	3	7	Δ  conc steps Jell-O	.365
	1 M	5	7	8	3	Dummy Δ pudding	.748
						Dummy Δ Jell-O	.748

differentially influenced by alcohol use. For example, alcohol use does not generally associate with “lack of planning” impulsivity, on which all BIS-11 subscales load highly [46]. In contrast, pre-potent response inhibition (often impaired in heavy drinkers) generally does not correlate with alcohol use [47].

We also failed to observe a shift in fat concentration preference, as was reported in rodents [17]. While the short length of the trial may also account for this null result, another possibility is that fat preference shifts are specific to dopamine disruption by a high fat diet. Along these lines, it would be interesting to assess whether alcohol perception is influenced by OEA supplementation. In fact we did find a trend for sweetness perception of the Jell-O's to decrease after PhosphoLean™ supplementation. This finding is intriguing given reports of a positive association between excessive alcohol intake and increased sweetness preference [48].

Although the findings of this preliminary study are encouraging there are a number caveats and limitations. First, the sample size was small (n = 22) and the trial length short, both of which could contribute to our inability to find effects on alcohol intake. We suggest an additional evaluation of outcomes after longer supplementation for future studies. Second, although we asked participants if they adhered to the supplementation instructions, we cannot rule out non-adherence. Third, OEA is synthesized in response to dietary oleic acid [15]. Since we did not administer food diaries we cannot rule out the possibility of dietary influences on OEA levels. This might have influenced our

results by increasing variance and negatively impacting sensitivity. However, it is also possible that OEA supplementation increased OEA levels, leading to preference shifts towards lower fat foods, which would potentiate the effects of supplementation. Although shifts in fat concentration preferences were not observed in our laboratory test, it is possible that food choices were influenced outside the laboratory. Such interactions would be interesting to investigate in future studies. Fourth, another source of intra and inter-individual variance may be the amount of NOPE in the dietary supplement. We did not evaluate the consistency and quality of NOPE in the dietary supplement. Future investigations should independently assess properties of PhosphoLean with liquid chromatograph or mass spectrometry. Fifth, we observed a trend towards an increase in depressive symptoms, in participants supplementing with PhosphoLean™. Although the increase was small, it raises the possibility that mood disturbance could be a side effect of long-term supplementation in heavy drinkers. An increase in depressive symptoms has not been shown before, and was unexpected. In fact in the rodent model OEA decreases immobility in a model of behavioral despair [49] and in humans has been shown to reduce depressive symptoms [19]. One possible explanation for our discrepant finding is our use of a dosage that was slightly higher and a regimen that was slightly more frequent (180 mg NOPE across three equal doses daily, before lunch and dinner, and after dinner) than previous reports [19,20]. It is therefore possible that benefits could be achieved with lower doses that may have less chance of influencing depressive symptoms. These



**Fig. 2.** Correlation matrix for TLFB and Go/No-Go task (change in pre versus post-test). Color gradient indicates Spearman correlation coefficient. Cells with a solid outline indicate significant correlations ( $p < .05$ ). Scatterplots illustrate significant correlations, with solid circles depicting values for participants in the PhosphoLean™ group and open circles depicting values for participants in the placebo group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

caveats notwithstanding, the findings we report nevertheless suggest a novel mechanism for improving impulsivity and support further studies to evaluate OEA as a therapeutic target for alcohol disorders and alcoholism.

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