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A mind cleared by walnut oil: The effects of polyunsaturated and saturated fat on extinction learning

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ABSTRACT

The treatment of anxiety-based psychopathology often hinges upon extinction learning. Research in nutritional neuroscience has observed that the regular consumption of perilla oil (50% alpha-linolenic acid (ALA)) facilitates extinction learning in rats (Yamamoto et al., 1988). However, acute facilitation of extinction learning by oils rich in ALA has not been reported for rats or humans, though the acute consumption of rapeseed oil (10% ALA) has been observed to improve cognitive processing speed in humans (Jones, Sünram-Lea, & Wesnes, 2012). For this reason, the present laboratory work examined the effects of adding walnut oil (12% ALA) to a chocolate milkshake on the acquisition, generalization, and extinction of a fear-based prediction in young adults. It compared performance between subjects. The other participants consumed a similar milkshake with either an equicaloric amount of cream (saturated fat), or with no added fat (control). Acquisition and generalization of the fear-based prediction were similar for all groups. However, those who consumed walnut oil extinguished most rapidly and profoundly. Implications for extinction learning are discussed.

1. Introduction

Research on the influence of food and nutrition on psychological functioning, mental performance, and general well-being has gained increasing attention over the years (e.g., Gardener et al., 2017; Hardman, Kennedy, Macpherson, Scholey, & Pipingas, 2016; Kaplan, Rucklidge, Romijn, & McLeod, 2015; Rechenberg, 2016; Sarris et al., 2015). A major insight is that Western diets high in refined sugars and saturated fat are associated with cognitive impairments in humans. Especially deficits in hippocampal-dependent memory functions have been documented, even on the short term (Attuquayefio, Stevenson, Oaten, & Francis, 2017; Beilharz, Maniam, & Morris, 2015; Francis & Stevenson, 2013). Much less is known, however, about effects on the effects of macronutrients on the cognitive function of learning, which is the process of acquiring and modifying knowledge and behavior.

Learning is a necessary ability for adapting to the surrounding environment, and enables the avoidance of danger. For example, after a large German shepherd aggresses at a person, a fear response is acquired. Since dogs of this breed share a similar appearance, this fear can then generalize to other German shepherds. Fear can be constrained by extinction learning, as the fear for stimuli is inhibited when the latter are encountered in the absence of an aversive event. If these otherwise safe stimuli continue to elicit fear, and irrelevant predictions are not extinguished, debilitating disorders such as cynophobia (the extreme fear of all dogs) can develop. Though fear-based psychopathology has likely always existed, it is surprisingly prevalent in our modern society (Baxter, Scott, Vos, & Whiteford, 2013), and interventions designed to facilitate the extinction of fear are of considerable interest (Davis, Myers, Chhatwal, & Ressler, 2006).

The acquisition of fearful expectations, its subsequent generalization, and extinction have been studied extensively in the laboratory with human and nonhuman animals (for reviews see Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Hofmann, 2008). Excitatory learning is generally considered a pivotal determinant of both acquisition and generalization of fear, whereas perceptual discrimination acuity seems an important determinant of generalization in specific (Dunsmoor & Murphy, 2014; Dymond et al., 2015; Struyf, Zaman, Vervliet, & Van Diest, 2015). The extinction of fear involves the inhibition of original learning (Bouton, 2002). Even after extinction, first learned excitatory associations can spontaneously recover with time, be renewed with a change in context, reinstated through exposure to the outcome, and quickly reacquired (Bouton, 2002). As a form of inhibitory learning, extinction is particularly dependent on neuronal activity in the ventromedial prefrontal cortex (vmPFC) and (ventral)

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hippocampus (Barrett, Shumake, Jones, & Gozalez-Lima, 2003; Ji & Maren, 2007; Moscarello & Maren, 2018; Quirk, Garcia, & Gozalez-Lima, 2006), with neuronal activity in the basolateral amygdala being relevant to the extinction of fear (Quirk, Repa, & LeDoux, 1995; LeDoux, 2000, 2014). Augmenting glutamate NMDA receptor activity in any of these three structures through the microinfusion of D-cycloserine facilitates the extinction of fear, while the microinfusion of AP5 (D-amino-2phosphon-pentanoic acid), a selective antagonist of the NMDA receptor, inhibits it (Fiorenza, Rosa, Izquierdo, & Myskiw, 2012).

Research with rats has observed that environmental factors such as diet can change learning performance and/or the functioning of the PFC and hippocampus (e.g., Kanoski, Meisel, Mullins, & Davidson, 2007; Kanoski, Zhang, Zheng, & Davidson, 2010; Yamamoto et al., 1988). Rats on a Western style diet (high in saturated fat and refined carbohydrates) show protein changes in the hippocampus (Francis, Mirzaei, Pardy, Haynes, & Cornish, 2013), as well as decreases in brain derived neurotrophic factor (BDNF) in the ventral hippocampus and mPFC (Kanoski et al., 2007). The level of BDNF affects the number of NMDA receptors and thus receptor activity in the hippocampus (more BDNF results in more receptors) (Caldeira et al., 2007). Western style diets have also been shown to cause oxidative stress, weaken the blood brain barrier and result in neuroinflammation, especially in the hippocampus (for a review see Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014). Behaviorally, such diets result in impaired inhibitory learning by rats, including slower reversal learning (which requires discontinuing a previously rewarded discriminative response and responding to a previously non rewarded stimulus), poorer performance on go/no go olfactory discriminations (Thiebaud et al., 2014), generally poorer extinction, and less robust renewal (reduction in context specificity of inhibitory learning) (Asem and Holland, 2012). The effects of saturated fat on other brain structures appear less significant, and learning processes that are immune to hippocampal impairments (such as simple discriminations) appear insensitive (Davidson et al., 2012). Interestingly, and opposite to the effects of saturated fat, the consumption of a diet enriched with perilla seed oil (a polyunsaturated (PUFA) fat rich in omega-3 precursor alpha-linolenic acid (ALA)), speeds discriminative learning and facilitates extinction more than safflower oil (a PUFA rich in linoleic acid) or a chow control (Yamamoto et al., 1988). Significant diet dependent changes in brain glycolipids were not observed in this study; however, Poulose, Bielinski, and Shukitt-Hale (2013) has observed that the regular consumption of walnuts (another source of ALA) reduces oxidative stress and inflammation in rat brains relative to a chow control (for a review see Poulose, Miller, & Shukitt-Hale, 2014). Also acute improvements in cognition have been observed after ALA consumption. In humans, the consumption of rapeseed oil (also rich in ALA) has been observed to improve attention and processing speed more than a calorie-free placebo after 15 min (Jones, Sünram-Lea, & Wesnes, 2012). Working memory was not so quickly facilitated, though it improved an hour after oil consumption, an effect that was not observed in the placebo condition.

The purpose of the current study was to examine whether the acute consumption of walnut oil versus cream would differentially influence the acquisition, memory and extinction of a fear-based prediction. In order to assess this hypothesis, healthy young human participants who refrained from consuming food for 3 h, were administered high calorie chocolate milkshakes (395 kcal) enriched with either walnut oil, cream (source of saturated fatty acids; SFAs), or a baseline control with no added fat, and thus fewer calories (164 kcal). We chose to compare walnut oil to cream (rather than another PUFA or glucose) for several reasons. First, SFAs are metabolized like PUFAs (i.e., through lipolysis) and the resulting free fatty acids provide an equal amount of energy over time, yet do not directly energize the brain because they are not actively transported across the blood brain barrier (unlike glucose) (Gropper & Smith, 2013). Thus, if calories and speed of digestion were responsible for acute benefits in learning, the walnut oil and cream milkshakes should both similarly facilitate learning more than the low calorie control. Second, Deopurkar et al. (2010) observed that the acute consumption of cream significantly increases systemic inflammation (as measured by circulating endotoxins and cytokines), and intravenous injections of endotoxins result in temporary learning, memory, and mood impairments in humans (Reichenberg et al., 2001). Thus, the cream milkshake might actually result in poorer learning. Such an observation would be relevant to the literature on how Western diets affect cognition, especially since acute effects from a single Western style meal on learning and extinction have not yet been reported. Last, PUFAs are essential fatty acids whether or not they contain ALA, and they may generally improve learning relative to SFAs. ALA might result in the greatest improvement, but the difference might be too subtle to detect in an acute manipulation with limited participants.

Following milkshake consumption, participants completed filler activities for an hour before being trained on a task that required them to learn which stimulus predicted the appearance of an aggressive German shepherd dog image. The delay was meant to ensure that testing took place during the postprandial period (when differential inflammation would be present between milkshake groups). It also reduced the possibility that the hedonic value of the milkshake would affect motivation, and thereby influence performance.

Acquisition rate was expected to be faster and memory specificity for the predictive stimulus was expected to be better for those who consumed the walnut oil than the cream and control. The improved memory was expected to result in a narrower generalization gradient for those who consumed walnut oil. It was also expected that those who consumed the walnut oil would extinguish their expectations faster than those who consumed the cream and control. Given that the cream milkshake contained more calories, it was hypothesized that those who consumed it would perform better than the low-calorie control (Macht, 1996; Messier, Pierre, Desrochers, & Gravel, 1998; Wyon, Abrahamsson, Järtelius, & Fletcher, 1997); however, the calorie-based advantages of the cream milkshake might be attenuated by acute inflammation and no difference (or even an impairment) might also be observed.

2. Material and methods

2.1. Power calculation

A placebo controlled double blind pilot study examining whether saturated fat (cream or coconut milk) affects memory observed a large effect size ($d = 1.38$). An a priori power calculation using G-power revealed that with such a large effect size, with alpha set to 0.05 (two-tailed) a sample size of 15 would be required for 95% power (Erdfelder, Faul, & Buchner, 1996). However, a previous meta-analytic review reported a medium overall effect size ($d = 0.56$) for memory enhancement by glucose (Riby, 2004). Accordingly, we chose a sample size of 20 per group.

2.2. Participants

Sixty-two healthy participants were recruited from the University of Leuven. The data from three of these participants were not included in the final analysis because of 1) a technological problem, 2) failure to drink the entire milkshake solution, and 3) failure to follow directions. Of the remaining, 37 were female and 22 were male ($M_{age} = 19.89$ yrs; $SD = 2.46$; range 18–31 yrs). There were 9 female participants in the Control group, 11 in the Cream and 17 in the Walnut group (see Table 1). Two of the participants classified as having an underweight Body Mass Index (BMI = 16–18.5), 10 were overweight (BMI = 25–30), and the remaining were within the normal range (overall BMI: $M = 22.41$; $SD = 2.97$). The study was approved by the Social and Societal Ethics Committee of KU Leuven (ML9416), carried

Table 1
Means (SDs) per condition.

		CREAM	WALNUT	CONTROL	*p*
N (women/men):					
(pre-)acquistion & generalization		20 (11/9)	19 (17/2)	20 (9/11)	.003*
extinction		19 (11/8)	17 (15/2)	19 (8/11)	.004*
Age		20.55 (1.32)	20.68 (1.63)	22.65 (3.03)	.02*
BMI		21.52 (2.24)	23.62 (2.95)	22.31 (3.49)	.17
Mood disturbance total score (POMS)		8.78 (10.04)	6.42 (7.37)	11.41 (10.76)	.48
Dog aversion		2.80 (2.48)	3.32 (2.38)	3.05 (2.46)	.78
Drink ratings					
Likeability		4.20 (1.24)	3.11 (1.37)	4.35 (.93)	.004*
Sweetness		2.60 (0.99)	3.21 (0.98)	3.20 (0.95)	.07
Consistency		3.80 (0.95)	3.53 (1.02)	3.55 (1.05)	.65
Healthy		2.10 (0.79)	2.42 (1.02)	2.30 (0.92)	.64
Calories		1.95 (0.83)	2.00 (0.94)	1.95 (0.69)	.98
Predictive ratings (last trial of each phase)					
Pre-acquisition	CS+	2.35 1.93)	2.84 (2.34)	3.30 (2.08)	
	CS-	1.75 (1.86)	2.42 (2.01)	2.95 (2.58)	
Acquisition	CS+	8.60 (2.16)	8.05 (2.34)	7.35 (3.01)	
	CS-	0.50 (1.19)	0.68 (1.45)	0.85 (1.60)	
Generalization	CS+	5.20 (3.49)	4.79 (4.02)	4.95 (3.69)	
	CS-	0.55 (0.99)	0.68 (1.34)	1.20 (2.24)	
Extinction	CS+	2.89 (3.20)	1.18 (1.63)	2.16 (2.71)	

Note. *p*-values result from a Kruskas-Wallis one-way ANOVA for all variables except gender ratio's. Gender ratio was tested with a two-sided Fisher exact test contrasting the proportion of men in the walnut versus control groups. $^*p < .05$.

out in accordance with local ethics guidelines, and was in accordance with the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from each participant.

2.3. Design

Following a randomized, double-blind, placebo-controlled, between subjects design, participants who had abstained from consuming anything with calories, caffeine, and nicotine for 3 h were administered one of three solutions in the form of a chocolate milkshake.

2.4. Milkshakes

All milkshakes were matched for volume (250 mL) as well as for flavor and sugar (12 g) content through the addition of 16 g Nesquik® chocolate powder. The lipid solutions contained either 85 mL cream (Campina® brand whole cream 33% fat) or 30 mL walnut oil mixed with Galaxy® brand reduced fat, low-lactose milk. The placebo control consisted of only milk and chocolate powder. The lipid solutions were isoenergetic (395 kcal), with equivalent macronutrient proportions (approximately 31 g fat, 23 g carbohydrate, 7 g protein) whereas the control solution provided only 164 kcal (4 g fat, 24 g carbohydrate, 8 g protein). The cream solution contained 21 g saturated fat, whereas the walnut and placebo solutions contained 5 and 2 g, respectively. Solutions were administered in opaque cups, covered by lids and ingested through a straw. Solutions were prepared in the laboratory using a blender (Kenwood® smoothie 2GO SBO55 300 W) and were refrigerated prior to testing.

Five questions were posed to the participants to assess on a scale of 1–5 (1 = "not at all" and 5 = "definitely") whether they 1) liked the milkshake, 2) the milkshake tasted sweet, 3) had a pleasant consistency, 4) was made from healthy ingredients, and whether the milkshake 5) contained many calories.

2.5. Body temperature

A Braun Thermoscan® Ear Thermometer with ExacTemp Technology (IRT4520USSM) was used to explore body temperature via the ear at several time points to assess whether the predictive learning task was administered during the postprandial digestive period. Measurements occurred at the beginning of the experiment and then after 60 and 100 min, the latter two times corresponding to the beginning and end of the predictive learning task. As this measure was only explorative and beyond the scope of the present paper, it will not be further discussed.

2.6. Interim activities

In order to fill the time between the ingestion of the milkshake and the predictive learning task, participants were asked to solve twenty different Dutch five-letter word anagrams. Participants were encouraged to solve them until the experimenter told them to stop.

After completing the anagrams, participants were asked to watch a TED lecture by Dan Gilbert with Dutch subtitles called "The Surprising Science of Happiness" that was 21 min long. They responded to 16 multiple-choice questions about the video.

2.7. Mood measure

Immediately following the interim activities, the participants filled out the validated Dutch version of the Profile of Mood States questionnaire (Wald & Mellenbergh, 1990). This 32-adjective rating scale is used to assess current mood. Each adjective is rated on a 5-point scale that ranges from 0 = "not at all" to 4 = "extremely". Five mood scales can be summed separately, which include Tension-Anxiety, Depression-Dejection, Anger- Hostility, Vigor-Activity, and Fatigue-Inertia. Also a total mood-disturbance score can be calculated by taking the sum of the scores of the four scales reflecting negative mood and subtracting the score on the Vigor-Activity scale of this sum.

2.8. Predictive learning task

The experimental learning task was programmed with Affect 4.0 and was based on the generalization paradigm of Struyf, Iberico, and Vervliet (2014). The stimuli presented consisted of 9 lines that differed by angle dimension. The starting angle (A1) deviated five degrees from a horizontal line and the angle of each subsequent line was increased by ten degrees (A2: 15°, A3: 25°, A4: 35°, A5: 45°, A6: 55°, A7: 65°, A8: 75°, A9: 85°).

The CS+ was always A5. The CS- was counterbalanced; it was either A1 or A9.

The to-be-predicted outcome was a picture of an aggressively attacking German shepherd dog (see Fig. 1). This image was selected

Fig. 1. The fear-based predictive learning task used this picture of an aggressively attacking German shepherd dog as the to-be-predicted outcome.

because humans are generally averse to images of aggressive dogs (reflecting a possible evolutionary predisposition to fear large predators) (Gullone, 2000; LoBue & Rakison, 2013). Aversion to this image was not assessed before the learning task, but at the end of the experimental session by having participants rate "How scary was the dog?" with 0 = "Not at all" and 10 = "Extremely". On average, participants found the image to be mildly scary $M = 3.05$, $SD = 2.41$ (range from 0 to 8), though 10 participants reported that the dog was not scary. Regardless, the image was unlikely pleasant even for those who did not report it as scary, and learning to predict the presentation of this image likely activated the same neurobiological substrates as those found to be hyperactive in real-life situations of aversion (Phelps, 2006). Previous research has observed that even when participants are only told that one neutral cue predicts an aversive stimulus and another predicts safety (in the absence of any real contingencies) greater amygdala activation as measured by functional magnetic resonance imaging (fMRI) is observed during the presentation of the "aversively" conditioned cue (Phelps et al., 2001). Thus, predictive learning (whether it be fear-based or not) depends on common processes.

Line presentation was followed (250 ms) by the appearance of an 11-point predictive rating scale where 0 = "Certainly not an aggressive dog", 5 = "Uncertain", and 10 = "Certainly an aggressive dog". Participants were asked to report the probability that they would see the aggressive dog image by clicking on the scale using a mouse cursor. A red dot then appeared at the clicked location to confirm their rating. After 200 ms the tilted line and dotted scale disappeared from the screen and the outcome occurred (for 1500 ms) or not before the intertrial interval (3000 ms).

At the beginning of the computer task participants received onscreen information. They were informed that a number of figures would appear and that the picture of an aggressive dog would follow some of these figures. They were asked to learn to predict the occurrence of the aggressive dog.

The experimental design consisted of four phases: pre-acquisition, acquisition, generalization, and extinction. In every phase trials were presented at random, with the restriction of no more than two consecutive identical trials. The latter was not true for the extinction phase, since only one stimulus (CS+) was extinguished. During the pre-acquisition phase, the CS+ and the CS- were each presented three times without the outcome. In the acquisition phase, the CS+ and the CS- were each presented 12 times; the CS+ was co-terminated with the outcome on eight of its twelve presentations. The generalization phase consisted of three identical blocks. Each generalization block consisted of one presentation of each of the seven generalization stimuli, two presentations of the CS+ (50% reinforced), and two presentations of the CS-. The GSs and the CS- were never followed by the outcome. The extinction phase consisted of twelve identical trials: a presentation of the CS + that was never followed by the outcome. Expectancy ratings were collected on all trials throughout the experiment.

2.9. Procedure

Upon arrival, participants confirmed their adherence to the aforementioned restrictions and then consented to the experiment. They were randomly allocated to a group. Their body temperature was measured and they were administered their milkshake solution. Following consumption, they answered the milkshake related questions, provided demographic information and then waited for 15 min so that the digestion of the nutrients could begin. Following this interval, participants engaged in the filler activities. They then completed the POMS and started the computerized predictive learning task (see Fig. 2).

The total duration of the experiment was approximately 100 min. Testing was conducted during the day and time of testing was balanced across groups.

2.10. Data analysis

Differences between the three groups in age, BMI, total mood-disturbance score, drink and aversiveness ratings of the dog picture were analyzed using Kruskas-Wallis non-parametric one-way ANOVA, as these variables were not normally distributed. Scores on the separate mood subscales of the POMS were not analyzed as they were heavily zero-inflated with e.g. a median value of zero for the depression scale.

The total number of anagram problems solved by the participants and accurate responses made regarding the video were analyzed using one-way analyses of variance (ANOVA) for independent samples.

Since the stimuli were counterbalanced across participants, the data for the pre-acquisition, acquisition, and generalization phases of the predictive learning task were first collapsed to obtain the within-subjects factor of Stimulus (CS-, GS1, GS2, GS3, CS+, GS4, GS5, GS6, GS7). The CS+ was always equal to A5.

The predictive ratings were analyzed for each phase (habituation, acquisition, generalization, extinction) separately using repeated measure ANOVAs (RANOVAs) with Trial and Stimulus as within subject factors and Group as a between subject factor. For extinction, there was no Stimulus factor included as only the CS+ was presented during that phase. Partial êta squared (η_p^2) will be reported as effect size. STATISTICA 12.0 was used for all analyses.

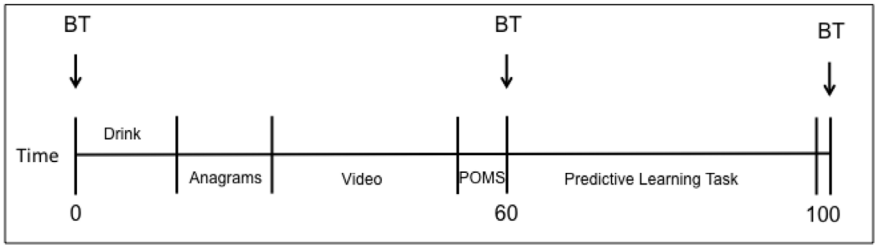

Fig. 2. Procedural schema. Following drink consumption participants answered demographic and drink related questions, after 15 min, participants worked on the anagrams for 10 min, watched the video and answered questions for 25 min, and then immediately after completed the POMS. The Predictive Learning task began 60 min after the milkshake had been administered. Body temperature (BT) was assessed around minutes 0, 60 and 100.

3. Results

3.1. Differences between groups

Table 1 provides information for each group on gender distribution, age, BMI, mood disturbance score, dog aversion ratings, and ratings on each of the five questions about the drinks (milk shakes). Group differences were present for three variables. First, gender was not equally distributed across groups, as the walnut group counted only 2 (10,5%) men compared to 9 (45%) and 11 (55%) men in the cream and control group, respectively. Second, the control group was about 2 years older than the walnut and cream groups; this effect was driven by two relatively 'older' participants aged 28 and 31 years old in the control group, as groups did no longer differ significantly without these two 'older' participants in the sample. Third, the walnut milk shake was liked less than both other milk shakes. Groups did not differ on the following ratings: mood-disturbance score (POMS), dog aversiveness ratings, and perceived sweetness, consistency, health value and number of calories of the milk shake drinks. The number of anagrams solved did not differ by group F (2, 56) = 0.14, p = .87. Response accuracy to the video related questions was similar across milkshake groups, F (2, 56) = 0.71, p = .49.

3.2. Predictive learning task

In case effects of Group on the predictive rating task were observed, additional analyses were run to explore to which extent the observed effects of Group on the predictive ratings could be driven by the significant between group differences in gender distribution, age, or likeability ratings of the milk shake.

In such cases, three extra analyses were run. First, we ran a RANOVAs with likeability rating as a covariate. Second, we re-ran the RANOVA excluding the two oldest participants (thus, without any age difference between group). Third, it was tested whether the observed effects of Group remained when only women were included. As the walnut group counted only 2 men, our sample was obviously underpowered to add gender as a variable in the model.

3.2.1. Pre-acquisition

We conducted a RANOVA with Trial (three levels), and Stimulus (CS + vs. CS-) as within-subjects factors, Group (Cream, Walnut, Control) as the between-subjects factor (see Fig. 3). There was a significant effect of Trial F (2, 112) = 29.55, p < .001, η_p^2 = 0.35. There was no main effect of Stimulus F (1, 56) = 2.11, p = .15, η_p^2 = 0.04. The only significant interaction observed was between Trial and Group F (4, 112) = 2.88, p = .03, η_p^2 = 0.09, reflecting a faster habituation by those in the Cream group. The remaining interactions were not significant, all Fs < 1.1.

3.2.2. Acquisition

We conducted a RANOVA with Trial (12 levels) and Stimulus (CS + vs. CS-) as within-subjects factors and Group (Cream, Walnut, Control) as the between-subjects factor (see Fig. 3). This analysis revealed a main effect of Stimulus F (1, 56) = 204.51, p < .001, η_p^2 = 0.79, the CS+ was more predictive of the US than the CS-. A main effect of Trial was also observed F (11, 616) = 10.02, p < .001, η_p^2 = 0.15, and a significant Trial × Stimulus interaction F (11, 616) = 44.82, p = < .001, η_p^2 = 0.45, with a significant linear trend F (1, 56) = 164.44, p < .001, η_p^2 = 0.75. This evidences that the discrimination between the two stimuli (CS+ and CS-) increased across trials. None of the interactions with Group were significant, all Fs < 1.67. There was no main effect of Group F (1, 56) = 0.16, p = .85.

3.2.3. Generalization

We conducted a RANOVA with Stimulus (CS-, GS1, GS2, GS3, CS+, GS4, GS5, GS6, GS7) as within-subjects factor and Group (Cream, Walnut, and Control) as the between-subjects factor (Fig. 4). This analysis revealed a main effect of Stimulus, F (8, 448) = 37.95, p < .001, η_p^2 = 0.40, with a significant linear and quadratic trend, F (1, 56) = 38.12, p < .001, η_p^2 = 0.41, F (1, 56) = 94.33, p < .001 η_p^2 = 0.63. There was no Group × Stimulus interaction F (16, 448) = 0.56, p = .92, η_p^2 = 0.02. The shapes of the gradients were similar across groups (no linear or quadratic interaction effects were observed, all Fs < 1.9). There was no main effect of Group, F = 0.20.

3.2.4. Extinction

Four participants (Control: n = 1; Cream: n = 1; Walnut: n = 2) were excluded from the analysis of extinction rate. This is because they had entirely extinguished their expectation of the outcome during the generalization phase, and during the extinction phase they responded with 0 = “Certainly not an aggressive dog” on all trials.

With the data from the remaining participants (N = 55) we conducted a RANOVA with Trial (twelve extinction trials with CS+) as the within-subjects factor and Group (Cream, Walnut, Control) as the between-subjects factor (see Fig. 5). There was a main effect of Trial, F (11, 572) = 14.06, p < .001, η_p^2 = 0.21, with significant linear and quadratic trends, F (1, 52) = 32.89, p < .001, η_p^2 = 0.39 and F (1, 52) = 9.57, p = .003, η_p^2 = 0.16, respectively. There was a significant interaction between Trial and Group F (22, 572) = 1.55, p = .05, η_p^2 = 0.06 with no linear or quadratic trends, all Fs < 1.64. The Trial × Group interaction became F (22,341) = 2.07, p = .0004, η_p^2 = 0.12 when including only women; F (22,550) = 1.46, p = .08, η_p^2 = 0.06 when excluding the two oldest participants (aged 28 and 31) in the sample; and F (22,561) = 1.82, p = .01; η_p^2 = 0.07 when likeability of the milk shake (rating) was entered as a covariate in the model.[1]

Additional analyses using RANOVA were used to examine how inhibitory learning (extinction) differed between groups. It was observed that the pattern of effects was driven by the performance of those in the Walnut group. When comparing the Cream and Walnut groups, a significant effect of Trial F (11, 374) = 13.26, p < .001, η_p^2 = 0.28, and an interaction between Trial and Group F (11,374) = 2.31, p = .01, η_p^2 = 0.06 were observed. There was also a main effect of Group, F (1,34) = 5.32, p < .05, η_p^2 = 0.14. Those who consumed walnut oil not only extinguished their expectation more quickly, but also more profoundly. Similarly, when performance by those in the Walnut group was compared to the Control, an effect of Trial was observed F (11, 374) = 0.11.1, p < .001, η_p^2 = 0.25, and the interaction between Trial and Group approached significance F (11, 374) = 0.1.68, p = .08, η_p^2 = 0.05. There, there was no main effect of Group, F (1,34) = 2.53, p = .12, η_p^2 = 0.07. As such, those who consumed walnut oil extinguished their expectations more quickly, but not more profoundly. However, the latter is due to similarity in inhibitory learning during the first trials. When we compared the average response of the last 6 trials between both groups, we did observe a main effect of Group, F (1,34) = 6.67, p < .05, η_p^2 = 0.16. When performance by those in the Cream and Control groups was compared, only a significant effect of Trial was observed F (11, 396) = 5.44, p < .001, η_p^2 = 0.13, the interaction was not significant F (11, 396) = 0.78, p = .66, η_p^2 = 0.02.

[1] When not excluding those 4 subjects in whom extinction learning could not be tested because of a floor effect, the main effect of Group was F(2, 56) = 2.60, p = .08 and the Trial × Group interaction was F(22, 616) = 1.37, p = .12 when both genders were included. When including only women (N = 11, 17 and 9 for the cream, walnut and control group, respectively), the main effect of Group was F(2, 34) = 2.81, p = .07, and the Trial × Group interaction was F(22, 374) = 1.76, p = .02).

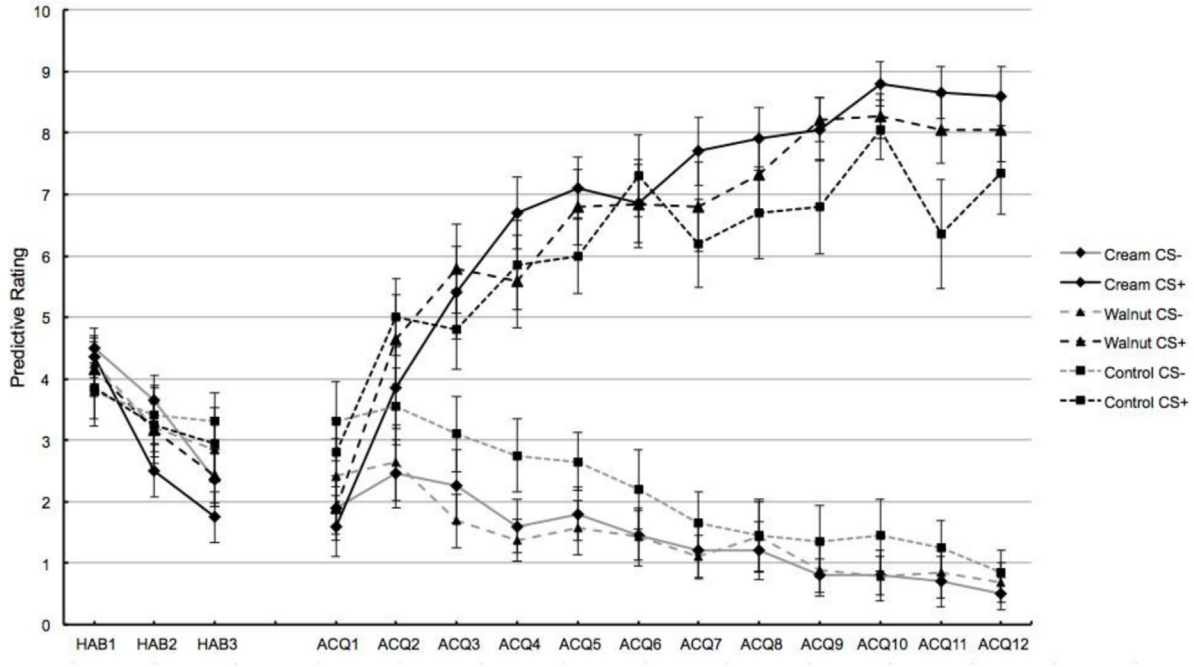

Fig. 3. The mean predictive ratings per group, stimulus (CS + and CS-), and trial during the habituation and acquisition phases of the fear-based predictive learning task. Error bars represent ± *SEM*.

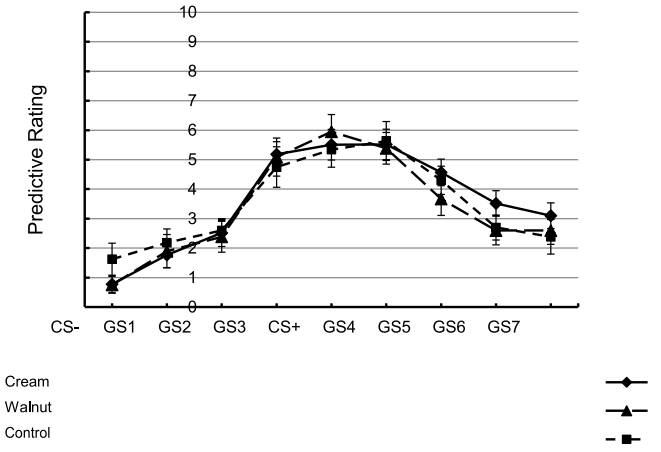

Fig. 4. The mean predictive ratings for all of the line stimuli presented during the generalization test phase of the fear-based predictive learning task. Error bars represent ± *SEM*.

4. Discussion

The current laboratory study was designed to assess whether the acute consumption of walnut oil could facilitate fear-based predictive learning by enhancing memory specificity, limiting stimulus generalization, and facilitating extinction more than an equicaloric amount of cream or low-calorie control. It was observed that walnut oil improved extinction learning.

Our failure to find differences in acquisition and generalization were unexpected. In retrospect, we hypothesize that acquisition may not have been affected because simple discriminative learning is relatively immune from dietary manipulations, whereas inhibitory learning appears to be quite sensitive (Davidson et al., 2012). The generalization of a fear prediction also appears to be immune to nutrient manipulations. Luyten, Schroyens, Nuyts, Luyck, and Beckers (2015) failed to affect generalization in rats with the administration of glucose, despite that glucose facilitates extinction (Schroeder & Packard, 2003). Stimulus generalization in humans is also not affected by sleep deprivation (Boddez, Struyf, Beckers, & Peigneux, 2014).

There were no performance differences for the interim activities (anagram resolution or recall memory for the video). This was not surprising since nutrients do not reliably improve the performance of easy tasks (Hoyland, Dye, & Lawton, 2009).

Though we argue that performance differences represent facilitation by walnut oil, the mechanism through which the acute consumption of walnut oil speeds extinction is not certain. Poulose et al. (2014) argue that walnut oil uniquely benefits cognitive function by maintaining synaptic plasticity, neuronal membrane stability, and promoting neurogenesis. However, these positive effects result from regular consumption, and it seems unlikely that the acute consumption of walnut oil improves inhibitory learning through these means. Jones et al. (2012), who observed acute cognitive facilitation by rapeseed oil, hypothesized that cognitive improvement might originate from nutrient dependent activation of the Vagus nerve.

The Vagus nerve (VN) is composed of approximately 80% afferent sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen. The sensory afferent VN fibers enter the medulla at the level of the olive, and travel through the tractus solitarius, terminating primarily in the nucleus tractus solitarius (NTS), providing widespread neuromodulatory control of subcortical and cortical structures including those implicated in fear learning. It has been reported that electrical stimulation of the Vagus nerve speeds extinction learning in rats (Peña et al., 2014). In humans, non-invasive, transcutaneous vagus nerve stimulation has been shown to facilitate extinction learning in predictive ratings, but not in psychophysiological indexes of fear (Burger et al., 2016; 2017). It seems thus plausible that walnut oil acutely facilitated inhibitory learning by activating the Vagus nerve through the release of gastrointestinal hormones such as cholecystokinin (CCK), for which there are receptors on vagal afferents (Ogawa et al., 2012). However, this can not explain why those who consumed cream did not outperform the control group, as long-chain saturated fats (which are present in cream) may also activate the Vagus nerve through CCK release (Lassman et al., 2010; McLaughlin et al., 1999).

The discrepancy in effects between the walnut oil and cream milkshakes may be related to greater systemic inflammation following the

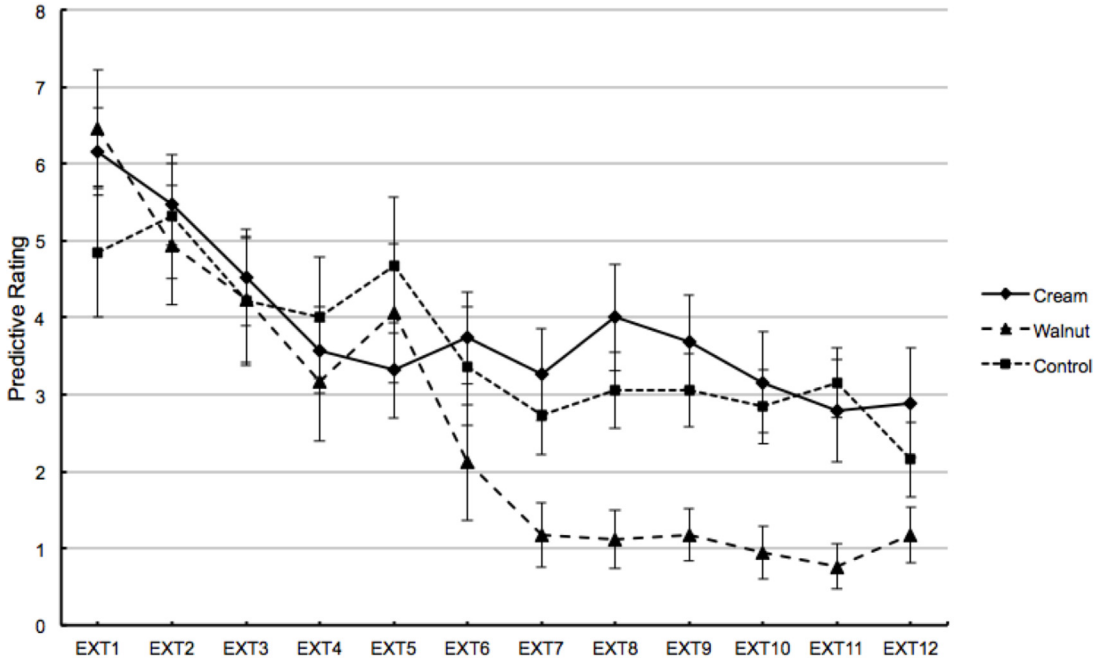

Fig. 5. The mean predictive ratings for the CS + across trials during the extinction phase of the fear-based predictive learning task. Error bars represent ± *SEM*.

consumption of the cream milkshake, which may in fact increase systemic inflammation and impair cognition (Grigoleit et al., 2011; Reichenberg et al., 2001). Deopurkar et al. (2010) reported that the consumption of 300 calories of cream increases circulating endotoxins unlike an equicaloric amount of glucose. Endotoxins (also called lipopolysaccharides, LPS) reside inside the outer cell membrane of gram-negative bacteria. The body is designed to mount an inflammatory response when endotoxins are detected and it does so by synthesizing inflammatory mediators (cytokines) and by stimulating cells to do the same (Gorbet & Sefton, 2005). Endotoxins are naturally introduced into the body by an exchange of body fluids, airborne particles, and food contamination. However, they can also enter the blood from within the body. This is because gram-negative bacterial colonies populate the intestines even in healthy individuals (Eckburg et al., 2005). These intestinal bacteria do not typically affect the body systemically because the intestines serve as an immunological barrier (Goto & Kiyono, 2012). But when this barrier experiences a partial breakdown, systemic and postprandial inflammation occurs (Berg, 1995).

The consumption of a single high fat Western style meal can compromise the intestinal immunological barrier and increase postprandial inflammation as measured by increased levels of circulating endotoxins and corresponding cytokines, a finding that cannot be attributed to food borne contaminants (Ghanim et al., 2009). These effects appear to be driven by the saturated fat component, as saturated fats impair endothelial function when consumed in large quantities (Nicholls et al., 2006; Tentolouris et al., 2008). Similar effects are not observed after the consumption of monounsaturated and polyunsaturated fats, especially those rich in animal sources of omega 3 fatty acids like fish or cod liver oil (Mani, Hollis, & Gabler, 2013), or plant sources (i.e., ALA) found in walnut or flax oil (Cortés et al., 2006; Jiménez-Gómez et al., 2009), which have anti-inflammatory properties.

The possibility that postprandial inflammation attenuates cognitive enhancement by saturated fat deserves further investigation. This is especially pertinent given that the inflammation of the central nervous system (i.e., neuroinflammation) is not only a consequence of a Western style diet, it is also the mechanism through which diet is believed to decrease BDNF, increase oxidative stress, and impair the BBB (Francis & Stevenson, 2013; Freeman et al., 2014; Glass, Saijo, Winner, Marchetto, & Gage, 2010). It is also likely the reason that associations between diet, systemic inflammation (measured by markers of inflammation found in the blood), cognitive dysfunction and psychopathology have been observed in humans (for reviews see Francis & Stevenson, 2013; Rosenblatt, Cha, Mansur, & McIntyre, 2014). The present study suggests that prior to severe dysfunction, changes in inhibitory learning may be observable.

All studies have their weaknesses and this one is no exception. A limitation of the present study is that the three groups differed with respect to some other variables that could theoretically underlie the reported effect of nutrients on predictive ratings during extinction learning. First, gender has been known to influence fear conditioning (Milad et al., 2006). As men were underrepresented in the walnut group, a potentially moderating role of gender could not be ascertained. As such, it remains unknown whether the observed facilitating effect of walnut oil on extinction learning, which was clearly present for the female participants in the present study, is generalizable to men. Second, future studies may want to control better for age, as the control group was slightly older than the other groups in the present study. However, it seems unlikely that the slightly older age of the control group accounts for the differences between groups in extinction learning, as there was also a difference in extinction learning between the walnut and cream groups without any age difference between both latter groups. Third, the walnut milkshake was less enjoyable. Although entering the likeability ratings as a covariate in the model did not change the pattern of findings, future studies may want to strive for drinks that are equally well liked. Another weakness is the low-calorie control. We included this condition to serve as a baseline, and to control for the hedonic effects of drinking a chocolate milkshake, and activation of Vagal afferents by volume distention (Steinert & Beglinger, 2011). However, because it had less fat and fewer calories, the effects it had on performance cannot be directly compared with those of the other milkshakes (that were equated for calorie and macronutrient content). Consequently, one could argue that the only useful comparison was between the high-fat milkshakes. Finally, although the milkshakes contained equal amounts of sugar, the sugar load used is considerable and may have affected learning performance as well. Interaction effects between effects of sugar and of lipids (ALA/saturated fat) cannot be excluded and whether the lipids would produce the same effects on extinction learning in the absence of the sugar load is still

subject for further research.

Despite the presence of other group differences, the results suggest that walnut oil led to faster and more profound extinction than cream. However, this should be interpreted with caution and future research with better control of the confounds present in the study is needed. Regardless of the mechanism, our finding provides further evidence that PUFA positively affects cognition relative to SFA, which is useful information for people who are making dietary decisions in the real world. The most obvious eventual implication of our research findings may be that in order to benefit maximally from exposure treatment, anxiety patients can choose or can be advised to consume more ALA and/or reduce the consumption of saturated fat. Possibly, the performance in any hippocampal-dependent learning situation may benefit from the same dietary intervention, as the hippocampus seems crucially involved in flexible behavior requiring an optimal integration of contextual information with existing representations and knowledge (Anacker & Hen, 2017; Rubin, Watson, Duff, & Cohen, 2014). However, further research will first have to replicate the present findings and to confirm that hippocampal functioning underlies the acute effects of different types of lipid consumption on extinction learning, or potentially more broadly, on cognitive and behavioural flexibility.

5. Conclusions

The current study is the first to demonstrate that the acute consumption of a chocolate milkshake rich in walnut oil (relative to cream or a low-fat control) results in a faster, more profound extinction of a fear-based prediction. In terms of fear learning, this means that nutrients can contribute to the extinction of irrelevant predictions. In relation to the clinical treatment of fear-based psychopathology, an implication of this finding is that exposure treatment (which relies on the extinction of fear) might be facilitated by replacing pro-inflammatory dietary nutrients (i.e., saturated fat) with anti-inflammatory ones (i.e., walnut oil). The contents of a patient's diet, and even the meal preceding a clinical session, could be important for recovery.

Author contribution statement

H.C.M. designed the study. D.S. designed the predictive learning task. P.B. recruited participants and gathered behavioural data. I.V.D. supervised the project. H.C.M., D.S. and I.V.D. analyzed the behavioural data. H.C.M. wrote the first version of the manuscript. B.D., D.S., L.V.O. and I.V.D. revised the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.appet.2018.04.004.

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