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