Omega-3 supplementation and the neural correlates of negative affect and impulsivity: A double-blind, randomized, placebo-controlled trial in midlife adults

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Abstract

Objective—In clinical trials, omega-3 fatty acid supplementation improves symptoms in psychiatric disorders involving dysregulated mood and impulse control, yet it is unclear whether in healthy adults omega-3 fatty acid supplementation affects mood, impulse control and the brain systems supporting these processes. Accordingly, this study tested the hypotheses that eciosapentaenoic (EPA) and docosahexaenoic (DHA) acid supplementation reduces negative affect and impulsive behaviors in healthy adults and that these changes correspond to alterations in corticolimbic and corticostriatal brain systems which support affective and impulsive processes.

Methods—Healthy volunteers (N = 272) consuming 300 mg/day or less of EPA and DHA were enrolled in a double-blind, randomized, placebo controlled clinical trial. Participants received either capsules providing 1000 mg of EPA and 400 mg of DHA versus identical appearing soybean oil capsules per day for 18 weeks. Negative affect and impulsivity were measured by questionnaire and ecological momentary assessment (EMA), as well as functional alterations in corticolimbic and corticostriatal brain systems evoked by standardized fMRI tasks.

Results—There were no group-by-time interactions for any questionnaire or EMA measures of mood and impulsivity. Likewise, no group-by-time interactions were observed for fMRI responses evoked within corticolimbic and corticostriatal systems.

Conclusions—In healthy adults with low intake of omega-3 fatty acids, moderate-dose supplementation for 18 weeks did not alter affect or impulsive behaviors, nor alter corticolimbic and corticostriatal brain functionality.

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Keywords

omega-3 fatty acids; clinical trial; negative affect; fMRI; impulsivity

Introduction

Although omega-3 (ω-3) polyunsaturated fatty acids are essential in the human diet,
Americans consume these nutrients in minimal quantities[1]. There is cross-sectional evidence
that deficiency of ω-3 fatty acids associates with depression, hostility, aggressive behavior,
and impulsivity in both psychiatric and non-psychiatric populations[2–13]. Clinical-trials also
show ω-3 fatty acids to have efficacy in some psychiatric disorders involving dysregulated
mood and impulse control, including bipolar disorder[14], borderline personality disorder[15],
major depressive disorder[16–17], and attention deficit hyperactivity disorder[18–19]. However,
meta-analyses of ω-3 fatty acid clinical trials in psychiatric populations report the behavioral
effects to be relatively small[20–22], and ω-3 fatty acid clinical trials assessing affect changes
in non-psychiatric populations have produced mixed results. In some studies, for example, ω
−3 supplementation has been related to decreases in negative affect[23–24], whereas other
studies have found no effect of ω −3 supplementation on negative affect or impulsivity[25–28].

In view of existing evidence, it appears possible that ω-3 fatty acids may alter brain
functionality prior to emergent or reliably detectable behavioral changes. In support of this
possibility, eciosapentaenoic (EPA) or docosahexaenoic (DHA) acids constitute 14–30% of
fatty acids in the phospholipids of brain tissue, particularly neuronal gray matter, compared
to less than 4% of fatty acids in plasma[29–30]. The types and amounts of dietary fatty acids
affect neural phospholipid concentration, with exchange between serum and brain
phospholipids in humans occurring by diffusion or active transport proteins[31–34]. Further,
placebo-controlled human neuroimaging studies show that ω-3 fatty acid supplementation
alters neural activity during cognitively demanding tasks in children and adults[35–37]. In these
studies, ω-3 fatty acid supplementation also improved cognitive performance, indicating that
alterations in neural functionality could link ω-3 fatty acids with behavioral change[35–37].

Accordingly, ω-3 fatty acids may relate to mood, impulsivity, and related behavioral
processes, in part, by affecting brain systems supporting these processes; namely,
corticolimbic and corticostriatal systems. Dysfunction of corticolimbic brain regions is
associated with mood disorders, such as major depressive disorder and bipolar disorder[38].
Corticostriatal regions are also associated with appetitive, reward-dependent behavior and
are strongly modulated by dopaminergic input[39–40]. Moreover, corticostriatal dysregulation
is associated with disorders such as attention deficit hyperactivity disorder[38]. Animal studies
have shown that fatty acid supplementation enhances production of neurotransmitters (e.g.,
serotonin and dopamine) that modulate corticolimbic and corticostriatal circuit
function [41–42]. Additionally, cross-sectional human research has shown higher ω-3 fatty acid
intake to associate with greater corticolimbic gray matter volume in healthy adults[43–46].

Despite long-chain ω-3 being concentrated in the brain and appearing to have treatment efficacy for several psychiatric disorders, no human placebo-controlled study has yet examined whether the effects of EPA and DHA on negative affect and impulsive decision-making are accompanied, and potentially accounted for, by longitudinal alterations in corticolimbic and corticostriatal functionality. Nor have any placebo-controlled studies examined whether EPA and DHA affect corticolimbic and corticostriatal functionality in the absence of observable effects on affective and impulsive processes. The present study tested for these effects in a double-blind, randomized placebo-controlled design in a healthy adult sample by measuring pre- and post-intervention corticolimbic and corticostriatal circuit activity changes that were evoked by standardized affect and reward-based functional magnetic resonance imaging (fMRI) tasks in conjunction with questionnaire and ecological momentary assessment of negative affect and impulsivity.

Methods and Materials

Participants

Participants were 134 men and 138 women between 30 and 54 years of age (see Figure 1 for Consort flow chart). A subset of participants (n = 121) participated in a neuroimaging protocol at baseline and post-supplementation. All participants were drawn from the Adult Health and Behavior Project – Phase 2 (AHAB-II) project. AHAB-II recruited volunteers through mass mailings of recruitment letters to individuals selected from voter registration and other public domain lists from the greater Pittsburgh metropolitan area. Participants were free of major chronic medical disorders and consumed 300 mg/day of EPA+DHA, as estimated from a food frequency questionnaire, had no seafood allergies, and were not currently taking fish oil supplementation. Participants were also screened to exclude those with current diagnoses of DSM-IV Axis-I disorders using the structured Mini International Neuropsychiatric Interview[47]. Further details regarding screening criteria for the AHAB-II study are provided in the text of Supplemental Digital Content 1.

Study Design

Data were generated from an exploratory randomized, double-blind and placebo-controlled trial at a single site using supplemented dietary intake of long-chain ω-3 polyunsaturated fatty acids in healthy mid-life adults. The trial was designed to test several putative primary prevention mechanisms, each linked to low dietary intake in published research: a) chronic systemic inflammation, b) low cardiac autonomic control, c) subtle cognitive functioning, and d) behavioral measures of reward-related impulsivity and negative affect. The trial's first published report presented findings related to chronic inflammation, along with details of the protocol and study design, adverse events and study blinding[48]. The current report describes affect outcomes and substudy functional MRI results. The trial is registered on ClinicalTrials.gov (RCT00663871). The investigation was approved by the Institutional Review Board of the University of Pittsburgh, and was conducted between June 2008 and December 2011. All participants provided written informed consent and were paid for their participation.

Intervention

Enrolled participants were randomized to one of two treatment conditions using R-Track, a secure web based program-wide clinical trial management system. Through minimization the marginal treatment distribution was balanced within levels of stratification factors of race (white vs. nonwhite), age (< 45 years, > 45 years), and sex (male, female). Participants in the fish oil condition (n = 134) received a daily dose of two 1000 mg fish oil capsules, together providing 1000 mg EPA and 400 mg DHA. This dose was chosen because it has been shown to substantially increase EPA and DHA levels in serum or plasma[49]. Participants in the placebo condition (n = 138) received a daily dose of two identical appearing 1000 mg soybean oil capsules. The placebo capsules contained 1% fish oil, and both supplements contained mint flavor to help maintain participant blinding. Capsules were distributed in weekly blister packs to assist with adherence, each labeled with the week number and a code for treatment assignment. The assigned supplements were distributed by a study nurse blinded to condition immediately after randomization. Through this standardized procedure, treatment allocation concealment was maintained. The treatment period was 18 weeks. Participants completed Ecological Momentary Assessment (EMA) recording days approximately two weeks before beginning supplementation. Due to scheduling reasons, follow-up EMA measures were completed approximately 16 weeks into supplementation, two weeks before the trial ended. Participants in the fMRI subsample began the fish oil trial on average two weeks after their baseline fMRI scan. Follow-up fMRI scans took place 16 weeks after beginning supplementation, two weeks before the trial ended.

Fatty Acid Composition of Red Blood Cells (RBCs)

Fatty acid composition of red blood cells (RBCs) was determined pre- and post-supplementation by first preparing hemoglobin-free RBC ghost membranes as previously described and stored at −70°C until further analysis[50]. Methods for lipid extraction and quantitative determination of fatty acid distribution have been reported elsewhere[47]. The intra- and inter-assay coefficients were 1.98 % and 3.88 %, respectively, for fatty acid at mean concentration of >300 nmol/mL, and 3.57% and 8.62%, respectively, for fatty acid at mean concentration of <150 nmol/mL.

Affect Measures

Negative affect—Negative affect was assessed using measures of depressive symptomatology and hostility. The original Beck Depression Inventory (BDI)[51] is a 21-item self-report measure having adequate discriminant validity[52], test-retest reliability (test-retest reliability = .73 to .90)[53], and internal consistency (Chronbach's alpha = .86) in clinical and non-clinical populations. Participants were asked to fill out the BDI reflective of their mood in the past week, including the day of testing. The cognitive, affective, and behavioral components of hostility were assessed using the 39-item version of the Cook-Medley Hostility scale[54–56]. This measure has reasonable test-retest reliability (10-year test-retest reliability 0.74), internal consistency (Chronbach's alpha = .83) and construct validity[56–57].

Impulsivity and aggression—The Barratt Impulsiveness Scale (BIS) is scored on a 4-point likert scale and consists of 30-items designed to assess control of thoughts and

behavior (e.g., acts without thinking)[58–60]. The BIS has high internal consistency (alpha coefficients 0.79–0.83) and high reproducibility (reliability coefficient 0.85)[59–60]. Aggression was measured using the total score of the Buss and Perry Aggression Questionnaire (BPAQ)[61], which demonstrates good test-retest reliability (test-retest reliability = 0.80) and internal consistency (Chronbach's alphas = .72-.85)[61].

Average Ecological Momentary Assessments—Ecological momentary assessments (EMA) allowed for measurements of negative affect and impulsive behavior, throughout the daily course of living; providing a more comprehensive measure of the intensities of different emotions, rather than relying on a summary (i.e., by questionnaires)[62]. EMA assessments were completed using a 4-day monitoring protocol (3 working days and 1 nonworking day). The monitoring protocol consisted of two 2-day monitoring periods, usually one period at the beginning of the workweek and another at the end of the workweek, with at least one non-monitoring day in between. The mean (standard deviation) number of observations for each item pre- and post- supplementation were 54.4 (8.64) and 55.53 (6.49), respectively. Participants carried a PDA (palm Z22, software: Satellite Forms) and answered a 43-item EMA questionnaire hourly on the PDA[63–64]. Each item asked participants to rate to what extent they were feeling the emotion. Answers corresponded with a 6-point Likert scale, 1 = strong "no" and 6 = strong "yes". Participants received extensive training and practice on the use of the PDA as well as feedback on compliance after completing a practice day. For this study, the negative affect (consisting of upset, hostile, nervous, afraid, angry, lonely, sad) and anger expression (consisting of annoyed, yelled) scores were used.

Neuroimaging Tasks and Measures

Participants engaged in two standardized affective and reward-based fMRI tasks designed to elicit activity changes in corticolimbic and corticostriatal brain systems[65–67] (for task details see Supplementary Text). In brief, the affective processing task required participants to match emotional facial expressions or simple geometric shapes to a target presented on a screen. The reward-based task required participants to make guesses that were rewarded or not rewarded with money.

Image Acquisition and Preprocessing—Functional blood oxygenation level-dependent (BOLD) images were collected on a 3T Trio TIM whole-body scanner (Siemens, Erlangen, Germany) using a 12 –channel phased-arrayed head coil. A small mirror was attached to the head coil to allow the participants to see the projector placed behind her or him while in the scanner. The functional BOLD image acquisition parameters can be found in the Supplementary Text.

The functional BOLD images were processed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK). Before analyses, BOLD images were realigned to the first image of the series by a 6-parameter rigid-body transformation, with the unwarp procedure in SPM being applied to adjust for geometric distortion due to movement. Realigned images were co-registered to each participant's T2-weighted structural image. Co-registered images were normalized by a 12-parameter

nonlinear and affine transformation to the International Consortium for Brain Mapping 152 template (Montreal Neurological Institute; MNI). Normalized images were smoothed by a 6mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Data Analysis

Sample Size—This study had a target sample size of 250 subjects (125 per treatment group) in order to achieve at least 0.80 power to detect differences in mean changes in negative affect and impulsivity from baseline to post-supplementation in terms of the standardized mean difference (d) as small as d = 0.4 between treatment groups. Sample size determination assumed a test-wise significance level of .01 when conducting two-sided hypothesis testing using linear contrasts within a repeated measures framework. ω −3 supplementation clinical trials using fMRI are limited and have mainly been focused on cognitive function, however, positive effects in these studies were seen with relatively small sample sizes (largest sample, total N = 36)[67].

Demographics—Baseline characteristics between groups were compared using one-way ANOVA for continuous data and chi-squared for categorical variables. Adherence to treatment was quantified as counts of returned pills and change in blood levels of EPA and DHA. Group differences in EPA and DHA over time were assessed using group (ω-3 fatty acid, placebo) by time (baseline, follow-up) ANOVAs. Of the 255 participants who completed the full trial there were missing data on the following outcome measures: BDI (n = 1), CMH (n = 6), BIS (n = 3), BPAQ (n = 6), all EMA measures (n = 10). An earlier paper from this trial demonstrated no group differences in adherence[48] between the two groups.

Affect and impulsivity analyses—Total scores for each of the questionnaires was used. Averages were created for EMA by creating an average for each day of assessment. Treatment differences between groups for all affect measures were examined using a series of group (ω-3 fatty acid, placebo) by time (baseline, follow-up) ANOVAs. Intention-to-treat (ITT) analyses, including all participants randomized into the trial, were conducted using linear mixed effects modeling where condition was included as a fixed factor[19]. These methods handle missing data points for the dependent variable without the use of listwise deletion.

Post-hoc sensitivity analyses—Mixed design ANOVAs were conducted examining if there were gender x treatment group x time interactions. Additionally, a series of bivariate regressions were run between change in DHA and EPA blood levels (level at follow-up minus baseline level) and affect variables (level at follow-up minus baseline level). Lastly, additional sensitivity analyses using the last observation carried forward method examining the effects of the trial on the main outcome variables were conducted. All affect related statistical analyses were performed using SPSS 21 (IBM Corp., Armonk, NY).

fMRI analysis—One-way ANOVAs were conducted to examine differences between the participants who had both fMRI and affect measures (n = 121) compared to those who just had affect measures (n = 146). After preprocessing, linear contrast images reflecting relative BOLD signal changes (i.e. Faces vs. Shapes; Reward vs. No Reward) were estimated for

each participant. To this end, task conditions were modeled with rectangular waveforms convolved with the default SPM hemodynamic response function (HRF). Contrast images were then generated by general linear model (GLM) estimation using an explicit brain mask and incorporating outlier weighting using the Robust Weighted Least Squares toolbox (v3.1; http://www.icn.ucl.ac.uk/motorcontrol/imaging/robustWLS.html). Before estimation, low-frequency BOLD signal noise was removed by high-pass filtering (128sec cut-off). Finally, regression vectors derived from the realignment step were included in the GLMs to account for BOLD signal variance attributable to head movement. Individual contrast images were then submitted to group-level, one-sample t-tests. Main effects for task at each visit were conducted using one-sample T-tests comparing the conditions (Faces vs. Shapes; Reward vs. No Reward). Group (ω-3 fatty acid; placebo) x time (visit 1; visit 2) interactions were examined using a mixed design ANOVA for both tasks. We first performed *a priori* region of interest analyses focusing on the amygdala for the affective task and the ventral striatum for the reward-based task. The amygdala and ventral striatum are core components of the corticolimbic and corticostriatal circuits, respectively, and are most reliably engaged by these tasks[65–66]. These *a priori* analyses were supplemented with whole brain voxel wise analyses to examine corticolimbic and corticostriatal responses outside of our ROIs. See Supplemental Digital Content 2 for description of ROIs. Family-wise error rate (FWER) threshold of 0.05 and cluster threshold of k   20 were employed in all imaging analyses.

Participant blinding and side effects—Study staff assessed side effects by calling participants during Week 2 and Week 12, and at a brief appointment during week 7. At the end of the trial participants were asked to guess what group they were assigned to. Differences between groups in reported side-effects and correctly guessing their assigned group were analyzed using chi-square tests.

Results

Of the original 272 participants, 255 completed the full trial. There were no significant differences between groups in demographic characteristics (Table 1). There were significant group (ω-3 fatty acid, placebo) by time (pre-, post-) interaction for red blood cell content of DHA and EPA. Specifically, supplementation increased EPA by 322% and DHA by 41% while levels did not change in the placebo group (Table 2).

Measures of affect, impulsivity, and aggression

Relative to placebo, the ω-3 fatty acid group did not show any significant changes in questionnaire or EMA measures of negative affect or impulsivity/aggression, p's > .20 (Table 3). There were main effects of time for BDI and EMA hostility scores, wherein participants in both groups reported less hostility and depressive symptomology in post-test compared to pre-test values. The ITT, utilizing the entire sample who enrolled in the study (N = 272), produced similar results for all dependent variables.

Sensitivity Analyses

Additional post-hoc analyses examining potential interactions with gender for each of the measures of affect and impulsivity/aggression were conducted. There were no significant

interactions. Change scores were calculated for both EPA and DHA blood levels and all questionnaire and EMA measures. Bivariate correlations between EPA and DHA change scores and change scores of all questionnaire and EMA measures were run. There were no significant correlations between EPA and DHA blood levels and any of the affective measurements. All results remained the same for main trial outcomes when using the last observation carried forward method.

Functional measures

There were no differences on any demographic variables or affective measures at either pre- or post- intervention between the sub-sample participating in the fMRI protocol and those with only affective measures (p's > .20). Both fMRI tasks evoked the expected main effects (groups combined) on functional activity changes pre- and post-intervention (see Figure 2, Supplement Table 1). Relative to placebo, ω-3 fatty acid supplementation did not change corticolimbic activity in response to the affective task in either ROI analyses or supplemental whole brain analyses. Similarly, there were no group-by-time differences in corticostriatal activity changes in response to the reward-based task in either ROI analyses or supplemental whole brain analyses.

Participant blinding and side effects

Overall, 33% in the fish oil group and 28% in the placebo group guessed their treatment assignment correctly ($p = 0.58$). Compared to those on placebo participants receiving fish oil reported somewhat more "fishy belch or aftertaste" and "loose stool, bloating or gas pains," but less "minty belch or aftertaste." No serious adverse events were reported by any participants enrolled in the trial (completed or not). Additional detail on these analyses have been reported previously[48].

Discussion

Low dietary intake and low blood levels of ω −3 fatty acid consumption are associated with negative affect and impulsivity in both psychiatric and non-psychiatric populations[2–13]. Placebo controlled clinical trials demonstrate that fish oil supplementation can reduce symptoms in a number of psychiatric illnesses (e.g., depressive symptomology, aggression in borderline personality disorder)[14–18]. However, no study has yet examined if such supplementation reduces negative affect and impulsive decision-making in parallel with changes in the functionality of brain systems implicated in affect regulation and appetitive or reward motivation. This study aimed to address this possibility in a non-psychiatric sample of adult community volunteers not currently taking medication that could alter neural activity. The present study further used comprehensive measures, both questionnaire based and EMA, to assess affect and impulsivity before and after the intervention. While the ω −3 fatty acid group had significant increases in levels of both EPA and DHA as part of the trial, there were no significant changes in negative affect or impulsivity. Additionally, there were no intervention-related alternations in task-evoked corticolimbic or corticostrital activity in the ω-3 fatty acid group compared to placebo group.

To date, the current study is the largest ω −3 fatty acid supplementation trial to assess neural functionality pre- and post-intervention and the only such trial to our knowledge to use fMRI with affective-related changes in a non-psychiatric, adult population[67]. In a randomized, placebo-controlled study, children (N = 33) who received low (400 mg) or high (1200 mg) DHA supplementation increased functional activity in the frontal and occipital lobes during a cognitive task relative to children in the placebo group[35]. ω −3 fatty acid supplementation increased bold signal activity during a cognitively demanding task in older adults (N = 21) with memory impairment[36]. In a double-blind, counterbalanced, cross-over study of 13 young adults EPA-rich supplementation was associated with faster reaction times on a Stroop task and less functional activation in the anterior cingulate cortex and increased activation in the precentral gyrus during the task[37]. These initial studies suggest ω −3 supplementation can alter neural function during cognitively demanding tasks. However, a recent study demonstrated that in children with ADHD and age-matched controls ω −3 supplementation improved parent-rated attention, but did not alter measures of brain activity or cognitive control[19]. None of these studies assessed measures of affect or function of the corticolimbic and corticostriatal circuits.

It is somewhat surprising that previous studies have not sought to examine the neural correlates of ω −3 fatty acid related changes in affect. Several sources have linked fatty acid deficiency to negative affect[2–7]. Accordingly, the current study attempted to extend these observational and preclinical studies. Cross-nationally, low seafood consumption is associated with a high lifetime risk of depression[2]. Within populations, low fish consumption is associated with heightened odds of both depression[3–4] and hostility[5]. Low concentrations of specific ω −3 fatty acids in plasma and red blood cell membranes are found in those with clinically significant depression or depressive symptoms[6–7] and violent or aggressive behavioral tendencies[8, 68–69]. In two different cohorts of approximately 100 generally healthy volunteers, serum EPA and DHA concentrations co-varied with normative variability in depressive symptoms and self-reported impulsivity[13, 70]. Clinical trials assessing affect changes in non-psychiatric participants have produced mixed results. In some studies, ω −3 supplementation has reduced anger[23], anxiety[23–24], and depression[23], while other studies have found no effect of on negative affect or impulsivity[25–28]. The current randomized and placebo-controlled ω −3 supplementation assessing negative affect impulsivity in a healthy population is the largest to date, and the first trial to assess both negative affect and impulsive behavior throughout the course of daily living pre- and post-intervention by EMA.

The trial is not without limitations. Participants consumed some ω −3 fatty acids before the trial began. They had a mean EPA+DHA intake near the US adult average of about 100 mg/day[45]. However, this amount is well below the recommended minimum consumption of 250 or 500 mg/day and did not differ between placebo and intervention group. It is possible that our observations were influenced by the exact dosage of EPA and DHA chosen here, as well as the duration of supplementation. There is some evidence that EPA and DHA have differential effects on different biological and behavioral outcomes[71]. Meta-analyses of trials of ω −3 on depression, for example, have suggested that EPA may specifically have therapeutic benefits for depression[72]. The current trial provided 1000mg/d of EPA and 400 mg/d DHA. The quantity was chosen to approximate the upper limit of what might be

consumed through dietary measures (with greater amounts constituting "pharmacologic" doses), and the ratio reflecting that of fish oil capsules widely used internationally. We also note that ω −3 acid supplementation has been reported to have measureable mood effects in patient populations[72] . It is possible that due to slow brain turnover ω −3 acid supplementation may also result in similar outcomes among healthy adults if they given in larger doses for longer periods of time. In addition, mean scores for depressive symptomology were low and it could be argued that a "floor effect" had been reached. However, there was a range in total BDI scores at baseline (Range: 0–24) and follow-up (Range: 0–19) and in BDI change from baseline to follow-up (Range: −14 – 9). Similar ranges were seen for other main variable outcomes. Additionally, the concept of impulsivity could be seen as trait rather than state. Therefore, it could be argued that one cannot directly reduce impulsivity[73-74]. However, recent short-term interventions have shown that certain interventions are able to reduce impulsivity. Finally, as study participants had to meet a large number of enrollment criteria, the findings may not be completely generalizable to the average adult population.

In summary, this randomized and placebo-controlled trial in healthy adults found no effect of 1400 mg per day of EPA+DHA supplementation for 18 weeks on corticolimbic or corticostriatal brain activity in healthy adults. Additionally, in line with some recent literature, there was no effect of supplementation on negative affect or impulsivity[25–28]. Future research may be needed to examine higher doses of supplementation and possibly psychiatric populations exhibiting clinical alternations in neural activity linked to dysregulated mood and impulsivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acronyms used in text

EPA	Eciosapentaenoic acid
DHA	Docosahexaenoic acid
EMA	Ecological momentary assessment
ω-3	Omega-3
fMRI	functional Magnetic Resonance Imaging
BDI	Beck Depression Inventory

BIS	Barratt Impulsiveness Scale
BPAQ	Buss and Perry Aggression Questionnaire
BOLD	Blood oxygenation level-dependent
FWER	Family-wise error rate
GLM	General linear model
HRF	Hemodynamic response function

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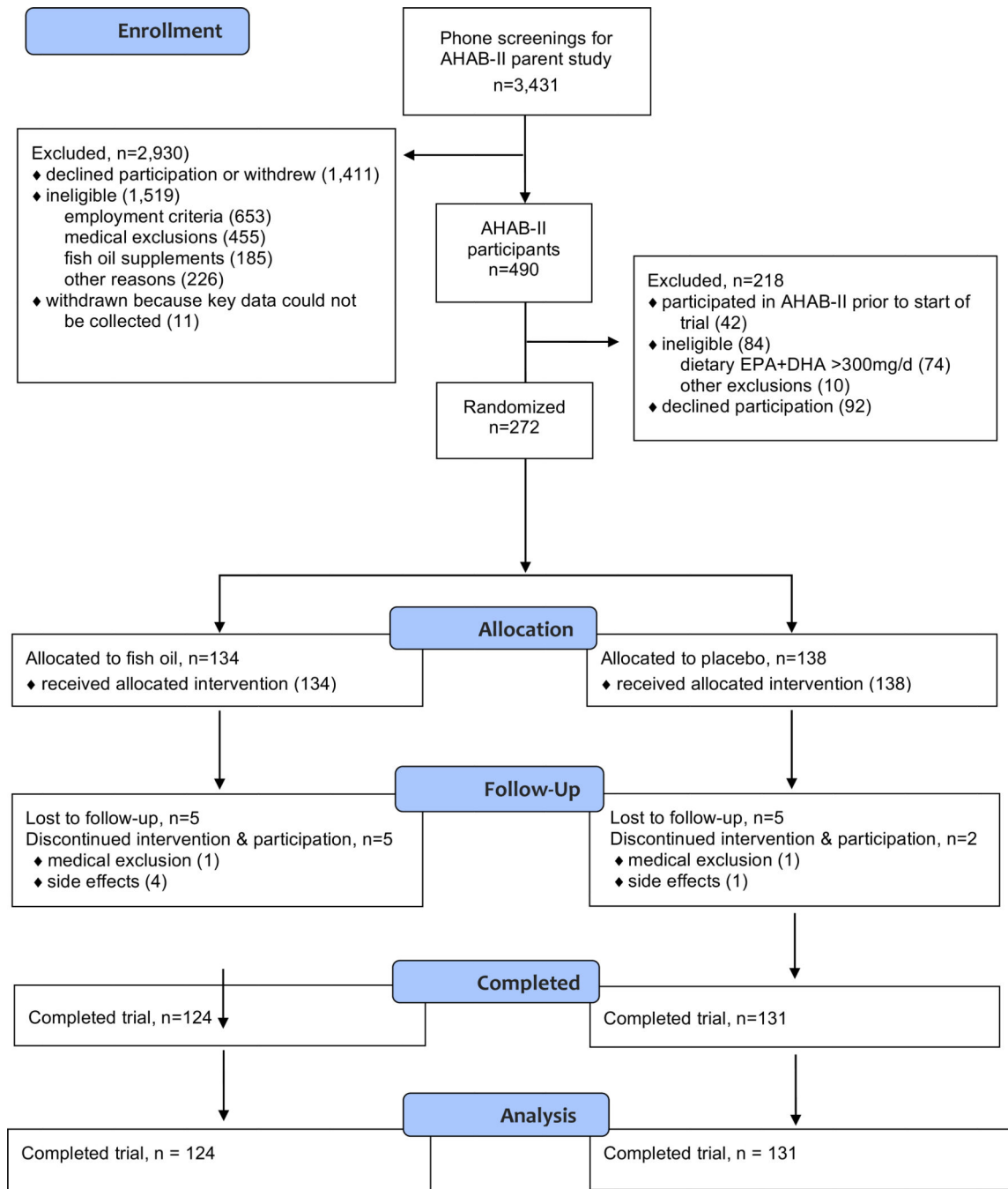
Figure 1.
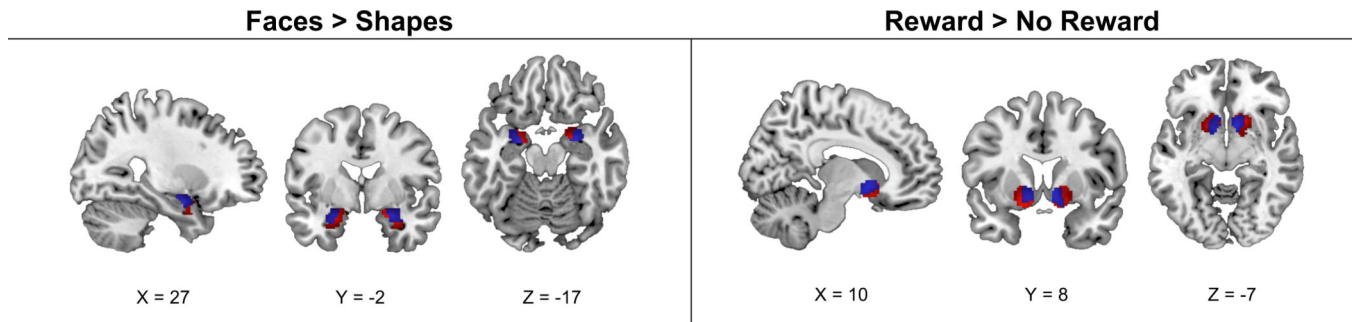Consort flow diagram of trial.

Figure 2.
Clusters of relative BOLD activation at time 1 (in red) and time 2 (in blue) within the amygdala and ventral striatum regions-of-interest, as revealed by the Faces vs. Shapes (affective task) contrast and Reward > No Reward (reward task) contrast at FWE 0.05 and k 20 voxels. FWE, family-wise error rate. Coordinates are displayed in MNI space.

Table 1

Baseline characteristics of randomized participants (N = 255)

Characteristic	Fish Oil	Placebo	Difference Statistic
Age	43.09 (7.54)	42.47 (7.03)	$F(1,270) = 0.49$, $p = .48$
Sex			$\chi^2(1) = 0.001$, $p = .97$
Male	58	76	
Female	60	78	
Ethnicity			$\chi^2(4) = 4.18$, $p = .38$
White	109	116	
Black	21	22	
Asian	1	0	
Multi-racial	1	0	
Other	2	0	
BMI	27.53 (5.92)	26.71 (4.60)	$F(1,270) = 1.61$, $p = .21$
Years of school completed	16.54 (2.77)	16.80 (2.68)	$F(1,270) = .653$, $p = .42$
WASI IQ	112.50 (12.61)	112.89 (12.55)	$F(1,270) = .066$, $p = .80$

Table 2

Blood levels of EPA and DHA pre- and post-intervention

	Placebo		Omega-3		Main group effect, F	Main time effect, F	Group x time interaction, F
	Pre	**Post**	**Pre**	**Post**			
EPA	0.44 (0.24)	0.41 (0.18)	0.45 (0.25)	1.45 (0.75)	169.59*	173.49*	199.44*
DHA	2.42 (0.89)	2.43 (0.98)	2.48 (0.87)	3.49 (1.19)	26.75*	57.62*	55.01*

*
p < .05

Table 3

Measures of negative affect and impulsivity/aggression pre- and post-intervention.

	Placebo		Omega-3		Main group effect, F	Main time effect, F	Group x time interaction, F
	__Pre__	__Post__	__Pre__	__Post__			
Negative Affect							
BDI score[a]	4.47 (3.86)	3.79 (3.43)	5.01 (4.87)	4.21 (3.81)	1.10	13.40*	0.07
CMH score	16.47 (7.34)	16.54 (7.21)	17.77 (7.92)	17.44 (7.59)	1.47	0.21	0.51
EMA negative affect	1.88 (0.70)	1.82 (0.73)	1.86 (0.71)	1.80 (0.68)	0.03	3.49	0.01
Impulsivity/Aggression							
BIS total score	59.51 (8.44)	59.38 (8.86)	59.23 (8.50)	60.10 (9.39)	0.29	0.004	0.20
BPAQ total score	56.07 (14.21)	55.51 (14.17)	58.33 (16.27)	57.63 (17.31)	1.35	1.23	0.02
EMA anger expression	1.50 (0.64)	1.53 (0.69)	1.52 (0.66)	1.49 (0.66)	0.90	0.02	1.13

*
$p > .05$

[a]Original version of BDI used