Eating to dare - Nutrition impacts human risk decision and related brain function

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Abstract

Macronutrient composition modulates plasma amino acids that are precursors of neurotransmitters and can impact brain function and decisions. Neurotransmitter serotonin has been shown to regulate not only food-intake, but also economic decisions. We investigated whether an acute nutrition-manipulation inducing plasma tryptophan fluctuation affects brain function, thereby manipulating risk-decisions. Breakfasts differing in carbohydrate/protein ratios were offered to test changes in risk decision-making while metabolic and neural dynamics were tracked. We identified that a high-carb/protein meal increased plasma tryptophan which precisely predicted individual risk-shift. Critically, the link between plasma tryptophan and risk-shift depended on individual's fat-mass. Using fMRI, we further identified activation in the inferior parietal lobule during risk, of which activities 1) were sensitive to tryptophan fluctuation, 2) were modulated by individual's body fat mass and 3) further predicted the risk-shift in decision-making. Our results provide evidence for a personalized nutrition-driven-modulation on human risk-decision and its metabolic and neural mechanisms.

Keywords

fat mass, fMRI, inferior parietal lobule, macronutrient, tryptophan, risk decision making, serotonin

Introduction

Food intake profoundly impacts not only human physiological processes but can also change our behaviors. The macronutrient composition of a food modulates multiple biochemical processes, among others plasma concentrations of large neutral amino acids (LNAAs) that can pass the blood-brain barrier. Specifically, tryptophan is the precursor of neurotransmitter serotonin [1] (5-hydroxytryptamine, 5-HT). Across species, plasma tryptophan has been shown to be closely related to the brain serotonin level [2,3]. Importantly, a meal with a higher carbohydrate/protein ratio increases plasma tryptophan level [1,4], which presumably enhances brain serotonin level. A change in serotonin dynamics in the brain has been shown to impact specific brain functions and behaviors, ranging from food-intake to aversive processing [5,6]. Although this provided novel possibilities for neuro- and behavioral modification through nutrition intervention, so far empirical evidence is lacking [7].

Serotonin plays diverse roles in energy homeostasis ranging from food-intake behavior to adipose tissue activity [6,8]. Central serotonin inhibits food-intake and increases energy expenditure [6], whereas peripheral serotonin in adipose tissue upregulates energy storage and inhibits energy expenditure [9]. Studies have reported increased peripheral serotonin levels in obese animal models [9,10]. However, it is still unknown whether and how the meal-driven fluctuation of serotonin precursor tryptophan relates to body fat and to brain function.

The central serotonergic system is targeted in major neuropsychiatric treatments and has been shown to modulate decision making [11,12], but effects are mixed. By

serotonergic manipulation, some studies indicated that serotonin facilitates punishment processing and behavioral inhibition [13,14]. In line with this, a pronounced risk-, loss- or harm-avoidance was associated with enhancement of central serotonin [5,15-18]. However, other studies showed that serotonin increased risk-seeking or loss-chasing after manipulation of serotonergic systems [19,20]. Considering the complex roles of serotonin in energy homeostasis, a potential explanation is that serotonergic modulation on risk- or harm-aversion processing might be dose-dependent. Supporting this, Crockett and colleagues [5] has reported the application of an acute dose of citalopram (a selective serotonin reuptake inhibitor, SSRI) changed harm aversion in body-weight dependent manner. SSRI increased harm aversion in participants with lower body weight (high dose), whereas, this effect was reversed in participants with higher body weight (low dose). In line with this, individual's risk preference has been shown to depend on the physiological status, such as body energy reserve [21-23]. Specifically, both the metabolic states (fasting vs satiety) and energy reserves influenced individual's risk-processing during decision making [22,23]. Thus, the decisions taken in the brain may integrate internal state (i.e. energy reserve) and the environment (i.e. property of stimuli) [7], which may reflect the essential maintains of homeostasis thereby individual's adaptation to the environment. Taken together, individual energy reserve differences may modulate the impact of nutrition on risk behavior via serotonergic pathways.

In this study, we experimentally manipulated the macronutrient composition of a standardized breakfast in a double-blind within-subject study design and tested

whether a one-shot meal intervention can modulate risk preference. Importantly, we systematically merge the metabolic, neural and behavioral data to dynamically capture the nutrition-caused changes and their dynamics. To do so, we take into account the temporal dynamics of plasma tryptophan and body fat as gating factors. Furthermore, the changes in neural processing during the decision making as a function of macronutrient manipulation were captured by means of functional magnetic resonance imaging (fMRI). In line with serotonergic pharmaco-intervention studies showing that 5-HT modulated risk decisions, we hypothesized that the high-carb/protein ratio breakfast would also change the risk preference, that is predicted by the plasma tryptophan fluctuation. Furthermore, we tested whether this effect is mediated by individual differences in body fat mass. On neural level, we aimed to unveil brain regions, in which activity reflects the nutrition-driven changes in metabolism and behavior. To enable this, we searched for brain regions of which activity fulfills all three criteria: The activity of the brain region 1) codes the nutrition-induced changes in risk behavior, 2) tracts the dynamics in plasma tryptophan and 3) reflects the individual differences in body fat.

Results

The influence of macronutrient composition on plasma tryptophan

To investigate the relationship between nutrition intake, body composition and risk decision behaviors, as well as metabolism and brain mechanism underling, we designed the procedure a within-subject breakfast-manipulation followed by a risk

decision making task (see Fig 1A for the experimental procedure). First, we checked whether the different meals induce different changes in tryptophan temporal dynamics: large neutral amino acid (Tryp/LNAA) ratio, by computing a repeated-measures ANOVA with time (T1-T4) and meal session (high vs. low-carb/protein breakfasts) as within-subject factors. In line with previous studies, we observed a significant increase in plasma tryptophan after a high-carb/protein breakfast. Specifically, there was a main effect of condition [$F(1, 34) = 66.23$, $p < 0.001$], a main effect of time [$F(3, 102) = 10.99$, $p < 0.001$] and an interaction between condition and time [$F(3, 102) = 16.52$, $p < 0.001$] in tryptophan/LNAA ratios. Post hoc analysis revealed higher tryptophan levels after the high-carb/protein breakfast for all postprandial samples [T2: $t(34) = 7.24$, $p < 0.001$; T3: $t(34) = 8.32$, $p < 0.001$; T4: $t(34) = 8.06$, $p < 0.001$] (Fig 2A). We also observed in a repeated-measures ANOVA that the individual time course of blood glucose was significantly modulated by the respective macronutrient condition [session × time interaction; $F(7, 238) = 7.39$, $p < 0.001$] (Fig 2B). Contrary to tryptophan, the tyrosine increased with greater protein content of the meal (see results section in Supplementary Materials). For the other metabolic parameters [insulin, cortisol, ghrelin, and leptin], there were no significant modulation by session (S1 Table). In addition, to assess the insulin resistance/sensitivity of the participants, a Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was conducted and we found the mean score of HOMA-IR was 0.79 (0.42 - 1.50), suggesting that the participants were insulin sensitive.

Plasma tryptophan fluctuation is body-fat dependent

According to previous literature [9,24], we hypothesized that the individual difference in body fat mass would be associated with the macronutrient composition induced changes in plasma tryptophan. Indeed, we found a positive correlation between fat mass (mean ± s.d. = 13.78 ± 5.22 kg) and the temporal dynamics of tryptophan/LNAA ratio (△T3-T1) (F = 9.62, p = .004, r^2 = .23; $r_{spearman}$= 0.36, P = 0.033) (Fig 3A). In other words, healthy participants with greater fat mass showed a greater plasma tryptophan fluctuation after carbohydrate-rich food intake. However, we did not observe this effect with tyrosine (see results section in Supplementary Materials). Furthermore, the BMI did not predict the plasma tryptophan and tyrosine fluctuations (see results section in Supplementary Materials).

The plasma tryptophan impacts risk behavior, fully mediated by body fat mass

Next, we checked 1) whether the nutrient-driven plasma-tryptophan fluctuation drives the risk-shift and 2) whether this is mediated by body fat. The nutrition-driven tryptophan/LNAA fluctuation (high vs low-carb/protein breakfasts) significantly predicted individual risk-shift (F = 4.24, p = .047, r^2 = .11; $r_{spearman}$ = 0.38, P = 0.026) (Fig 3B). Given the correlation between tryptophan fluctuation and fat mass, we further tested whether the relationship between tryptophan fluctuation and risk-shift is mediated by individual's fat mass by performing a mediation analysis [25,26]. Indeed, the influence of tryptophan/LNAA change on the risk-shift was fully mediated by individual's fat mass (a = 0.46, SE = 0.14, p = 0.009; b = 0.37, SE = 0.21, p = 0.039;

ab = 0.17, *Z* = 2.23, *p* = 0.026; Fig 3D). Thus, the manipulation of macro-nutrient composition exerts its effect on participants' risk-preference via plasma tryptophan, depending on the individuals' energy storages. The mediation effect was stable also after controlling the plasma tyrosine fluctuation (see Results section in Supplementary Materials). Taken together, the macronutrient-driven modulation in tryptophan led to a shift in risk-aversion, a finding mimicking the effect of SSRI on harm-aversion [5].

The plasma tryptophan changes modulate neural signal in inferior parietal lobule (IPL)

We first tested the relationship between meal-induced plasma tryptophan fluctuation and brain activation changes during risk-processing. Here, in a whole-brain regression analysis, we searched for brain regions, that significantly reflect the inter-individual differences of meal-induced tryptophan dynamics, during risk processing (high vs. low risk gamble choices in high- vs. low-carb/protein). The result showed that the plasma tryptophan fluctuation significantly predicted the risk-related BOLD changes within the bilateral IPL (Left IPL: MNI x = -51, y = -42, z = 51, *t* = 5.20; Right IPL: MNI x = 30, y = -54, z = 42, *t* = 5.14; $p < 0.05$, whole-brain FWE corrected) (Fig 4A, Table 1, see also results section in Supplementary Materials for nutrient-induced BOLD changes in risk-processing).

Table 1. Tryptophan/LNAA fluctuation modulates BOLD changes in response to risk-processing.

Regions	Hemisphere	BA	Volume (voxel)	Peak MNI (mm)			Peak *t* value	*P*-value
				X	Y	Z		cluster(uncorr)
IPL/ angular gyrus/ SMG [a]	L	40,7	224	-51	-42	51	5.20	< 0.001
IPL/angular gyrus/ precuneus/ SPL [a]	R	40, 7	130	30	-54	42	5.14	< 0.001
OFC/ vmPFC	L	11	29	-30	42	0	4.40	0.047
MFG/ SFG	R	9, 8	64	39	33	33	5.30	0.006
MFG	L	9, 8	30	-30	21	42	4.42	0.044

BA, Brodmann's area; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute space; OFC, orbital frontal cortex; R, right; SFG, superior frontal gyrus; SMG, supramarginal gyrus; SPL, superior parietal lobule; vmPFC, ventromedial prefrontal cortex.
[a]Cluster-level family-wise-error (FWE) correction ($P_{FWE} < 0.05$).

Individual variation in body fat mass predicts risk-related activity in the IPL

Next, we tested whether body fat mass predicts neural responses to risk-processing, in a separate whole-brain regression analysis. Here, we searched for brain regions, that significantly reflect the inter-individual differences in fat mass, during risk processing (high vs. low risk gamble choices in high- vs. low-carb/protein). The individual differences in fat mass positively predicted the BOLD changes during risk-processing within the left IPL (MNI: x = -39, y = -51, z = 39; t = 4.65; p < 0.05, whole-brain FWE corrected) (Fig 4A, Table 2).

Table 2. Body fat mass predicts BOLD changes in response to risk-processing.

Regions	Hemisphere	BA	Volume (voxel)	Peak MNI (mm)			Peak *t* value	*P*-value
				X	Y	Z		cluster(uncorr)
IPL/ angular gyrus/ MTG [a]	L	40,39, 7	380	-39	-51	39	4.65	< 0.001
IFG/ MFG	L	9	74	-39	24	30	4.34	0.004

angular gyrus/ IPL	R	39	42	51	-69	39	3.65	0.021
MFG	L	8	41	-39	18	51	3.95	0.022
OFC/ MFG	L	11	27	-27	48	-9	4.57	0.056
ITG	L	20	29	-54	0	-39	3.76	0.049
IPL/ SMG	R	40	32	48	-42	42	3.47	0.040

BA, Brodmann's area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute space; MTG, middle temporal gyrus; OFC, orbital frontal cortex; R, right; SMG, supramarginal gyrus.
[a]Cluster-level family-wise-error (FWE) correction ($P_{FWE} < 0.05$).

Conjunction in the IPL predicted the individual shift in risk-preference

The preceding brain-physiology relationship analyses revealed very similar activation patterns in the relationship between nutrition-modulated brain responses during risk-processing and 1) nutrition-driven changes in tryptophan/LNAA reflection and 2) individual body fat mass. In the final analysis, we sought to identify the brain regions, of which activation codes all these elements by a whole-brain conjunction analysis (voxel level threshold $p < 0.005$ uncorrected and cluster size > 20). Indeed, the convergence of tryptophan dynamics and fat mass predicted risk-processing brain regions has been identified within the left IPL, dorsolateral prefrontal cortex (dlPFC) and orbital frontal cortex (OFC) (Figs 5A-5C). Therefore, these regions code the link between meal-induced plasma tryptophan fluctuation and risk-processing, depending on the individual fat mass.

We finally checked, whether the activation of the conjunction regions also reflect the individual responsiveness to nutrient-modulated behavioral change (risk-shift), by predicting the between-session risk-shift using the mean-extracted signals from these

three regions, which was indeed the case (the IPL [-39, -48, 42]: $r(32) = .35$, $p = .049$; the dlPFC [-39, 21, 33]: $r(32) = .43$, $p = .015$; the OFC [-30, 45, -3]: $r(32) = .38$, $p = .034$) (Figs 5D-5F).

Taken together, the high-carb/protein meal modulates risk-aversion, via plasma tryptophan fluctuation, depending on the individual body-fat. Our results suggest that this interplay in coded in the front-parietal network.

Discussion

Previous studies showed that the modulation of serotonergic system induces risk shift, a mechanism that may depend on energy reserve. In our study, we utilize nutrition intervention by manipulating macronutrient composition of a breakfast to induce changes in brain serotonergic system. Indeed, we observed significant changes on plasma tryptophan as metabolic measures, and that the meal-induced plasma tryptophan/LNAA changes significantly predict the changes in risk behavior, an effect that is gated by body fat mass. Furthermore, our neural results identified the BOLD changes in IPL as a function of risk-processing, 1) that reflected the meal-induced differences in plasma tryptophan fluctuation and 2) that correlated with individual fat mass. Also, the same activation patterns were found in dlPFC and OFC. More strikingly, the activation within sub-regions of the IPL, dlPFC and OFC further predicted individual differences in nutrient-modulated risk-shift. Taken together, these results deliver a strong evidence of macronutrient-driven changes in modulating metabolism, the brain and behavior, such that it closely mimics pharmacological

intervention driven changes.

Our results were consistent with previous studies showing differences in plasma tryptophan and tryptophan/LNAA ratios followed by food consumption in both animals and humans [1,3,24]. The dietary effects on brain serotonin system depends on 1) the concentration of free plasma tryptophan and 2) the ratio of tryptophan to the other LNAAs sharing the same transport for the blood-brain barrier [24,27]. On the one hand, the fasting tryptophan has been implicated to be negatively associated with individual's body mass [28] (see also results section in Supplementary Materials for our data), which may implicate the gating function of body fat in tryptophan utilization. On the other hand, the high-carbohydrate diet prompt brain uptake of tryptophan by inducing insulin which increases the uptake of other LNAAs into peripheral tissues, thereby decreasing their competition with tryptophan for brain uptake [2]. In our study, a significant increase in insulin levels after high-carb/protein meal (vs low-carb/protein) 0.75h after the blood glucose reach peak may indicate the possibility of carb-rich-meal prompted tryptophan brain-uptake via insulin release (see results section in Supplementary Materials). Furthermore, studies investigating the role of serotonin in energy homeostasis regulation have reported increased serotonin levels in obese animal models and revealed the serotonin-facilitation in lipid accumulation [6,9]. Our study found the macronutrient-driven changes in tryptophan/LNAA in relation to body fat, suggesting the body-fat-gated nutrient-modulation in tryptophan metabolism. Taken together, the nutrient-variation diets may offer a non-pharmacological approach with high ecological validity for

modulating the serotonin function in regulating decision behaviors, while gated by body composition.

Previous studies tackling role of serotonin on decision making (e.g., pharmacological intervention, tryptophan depletion), have delivered inconsistent results. Some studies demonstrated that 5-HT enhanced risk-, harm-aversion [5,18,29,30], as well as facilitated behavioral inhibition [13,14]. However, some studies showed no effects of serotonin-intervention in risk decision performances [31-33]. On the other hand, the other studies reported risk-prone and loss-chasing behavior with enhanced brain serotonin level [19,20]. These inconsistent effects may due to the complexity of serotonergic system itself [12], the efficiency of different manipulation methods for the 5-HT system [34,35] (e.g., SSRIs versus tryptophan depletion procedure, acute versus chronic manipulation), and the interaction between manipulation methods and individual characteristics [11]. For instance, in the study Crockett and colleagues report that the SSRI's impact on avoidance behavior is body-weight dependent [5]. Specifically, participants with lower body weight demonstrate risk avoidance due to the higher effective dose of SSRI, whereas participants with higher body-weight become risk prone due to the lower effective dose of SSRI. In line with this, we observe that the individual body fat significantly predicted the nutrient-induced risk shift. Analogous to Crockett and colleagues' study [5], lower body fat is linked to less tryptophan fluctuation and also let to risk prone after high vs. low carb/protein breakfast. On the other hand, whereas participants with higher body fat increased risk aversion as predicted by the greater enhancement of

tryptophan. Therefore, it seems to be that the body fat acts as a gate regulating the tryptophan fluctuation and thereby the meal's impact on the risk decision and brain function.

Alternative interpretation is provided by studies showing the influence of energy reserves on risk-sensitivity during foraging [22]. The animal's risk-preference during foraging as a function of metabolic reference point (e.g., energy levels of hunting individuals, the diet quality) was U-shaped [22]. In line with the theory, a human study showed postprandial increase of risk-preference in financial decisions compared to that in fasting state, which positively correlated with participant's energy reserves [23]. In light of these findings, our results can be interpreted as evolutionarily beneficial mechanism, such that in case of low energy reserve, higher carb-intake promotes more risk-prone behavior (e.g., foraging protein-rich food). Whereas with the high energy reserve, higher carb/protein intake encourages more cautious behavior, thus to balance the food-intake.

Recent meta-analysis and lesion studies have demonstrated the key role of the IPL, dlPFC and OFC in risky decision making [36,37]. Consistently, our results found that participants showed greater brain activation when making high vs. low risky options in IPL and possibly in OFC and dlPFC driven by nutrient-manipulation. Specifically, the IPL is implicated to modulate the level of uncertainty, which may relate to its role in judgments about probability and derivatives such as expected values [38]. Additionally, previous risk decision making studies identified the involvement of the inferior frontal gyrus in individual's risk-processing by comparing participant's

responses to stimuli with high vs low risk levels [39,40]. Interestingly, the front-parietal regions have been implicated with high density of serotonergic receptor neurons [12]. For instance, by manipulating the serotonergic system, studies revealed the changes in activities of the prefrontal cortex (PFC), OFC and striatum in gamble decisions [41-43], as well as enhanced activation of the dlPFC, OFC and parietal lobule in response for impulsive control [44,45]. Consistently, our results showed that those regions as a function of tryptophan fluctuation predicted risk-shift after nutrition-intervention.

Previous studies using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) suggested associations between body mass and 5-HT receptors density or transporter (SERT) availability in broad cortical regions (i.e., OFC, DLPFC, parietal lobule,) and subcortical regions (i.e., striatum and thalamus) [46-49]. Across normal-weight and obese people, positive correlations have been demonstrated between BMI, and global brain SERT availability, 5-HT_{2A} receptor binding across cerebral cortex, 5-HT_4 receptor binding in reward circuits [46,48,49]. The same brain regions reflecting tryptophan fluctuation and fat mass in our findings supported the findings above, suggesting the modulating role of body composition in serotonergic neurotransmission, or even the dysregulation of serotonergic system as a probable pathophysiologic mechanism in obesity. However, in another two studies the SERT availability showed no significant or negative association between non-obese and obsess subjects [47,49], which may implicate the lower reliability of the parameter BMI in predicting serotonergic system and risk decision behaviors.

In our study, we investigated only normal weight male participants without insulin resistant. However, according to previous studies, individuals with obesity showed greater impulsivity, diminished tryptophan circulation and metabolic response, as well as the increased insulin resistance [28,50,51]. Consistently, research further demonstrated the non-effective high-carbohydrate diet in raising tryptophan ratio in diabetic rats [52]. Therefore, further investigations are required to reveal the underlying mechanisms in diet induced tryptophan metabolism among clinical populations (e.g., obesity and diabetic patients).

Taken together our results deliver a novel perspective for how nutrition can induce brain and behavioral changes, by demonstrating how nutrition intervention induces neural and behavioral changes that mimic pharmacological intervention. Specifically, our data demonstrate the gut-brain interplay that depends on body energy homeostasis. This provides wide-ranging implication for the society, by offering evidence-based and personalized nutrition recommendation and opening a new avenue for possible treatment strategies for both metabolic and psychiatric clinical population.

Methods and materials

Participants

To investigate the relationship between nutrition intake, body composition and risk decision behaviors, as well as the metabolism and brain mechanisms underlying, we performed a randomized, two-session study in 35 males, normal-weight volunteers

(age, 23.82 ± 3.19 years; BMI, 22.96 ± 1.75 kg/m^2). Every participant underwent a medical screening to exclude metabolic abnormality. The medical screening consisted of a blood sample, a physical examination, and a questionnaire. Exclusion criteria were any abnormalities in the blood results or physical examination, any physical or psychological disease, shifted day/ night rhythm, being a high-performance athlete, BMI under 18 kg/m^2 or above 30 kg/m^2, smoking, or food allergies. 32 of these participants (age, 23.85 ± 3.20 years; BMI, 22.85 ± 1.78 kg/m^2) completed the two sessions of fMRI measurement successfully. All participants gave written informed consent according to the Declaration of Helsinki. The study was approved by the local Medical Ethical Commission of the University of Lübeck.

Experimental design

The study was carried out in a randomized, balanced, within-subject design during two sessions separated by at least 7 days (maximum 9 days) (Fig 1A). In both sessions, participants received equal-caloric breakfasts (850 kcal). On one day, a high-carb/protein (80% carbohydrates, 10% fats, and 10% proteins) breakfast and on the other day a low-carb/protein (50% carbohydrates, 25% fats, and 25% proteins) breakfast as control was given to the participants. Participants were instructed to consume the whole breakfast (see the Methods section of Supplementary Materials for further details on experimental design).

The study conducted in a research laboratory. At 0745 hours, body composition was assessed by air displacement plethysmography (ADP) using the BOD POD

system (BOD POD®, Cosmed, Fridolfing, Germany). Body mass was measured directly before subjects entered the chamber using an electronic scale connected to the BOD POD system. While measurements, subjects were sitting in the chamber wearing tight-fitting underwear and a swim cap. Two repeated measurements of body volume were performed. If values deviated more than 150mL, a third body volume measurement was done. Data were averaged and body composition parameters, i.e. body fat mass and fat free mass, were calculated according to manufacturer's software based on Siri's equation for body density (version 5.4.1; BOD POD®, Cosmed, Fridolfing, Germany). Thoracic gas volume was predicted. Before each measurement, a two-step calibration was carried out.

At 0815 hours, an intravenous catheter was inserted into a vein of the participant's non-dominant distal forearm and the baseline blood sample was obtained at 0830 hours. At 0845 hours, participants received breakfast according to the high- or low-carb/protein condition respectively. The blood samples drawn at 0830, 0900, 0915, 0930, 1000, 1030, 1130 and 1315 hours (Fig 1A). During the whole procedure subjects could either lie in bed or sit on a chair, but to leave the room or perform any type of physical exercise was not allowed.

At 1200 hours, participants were instructed to complete the risk decision making task with the fMRI scan. At 1300 hours, participants were guided to a different room where they completed a questionnaire battery including the PANAS [53], the Big Five Inventory (BFI-10) [54], and the behavioral inhibitory system/behavioral approach system [55]. These assessments were performed at 1145 hours because the maximum

difference in neurotransmitter precursor concentrations between conditions was expected to be present 3.5-4 h after the food intake [1,4]. Metabolic parameters in 1315 (T4) were considered and reported to ensure the nutrition-driven effects lasting until the end of the test battery including the risk task and several questionnaires.

Risk decision making task. All participants went through the risk decision making task in the MRI scanner and made repeated choices between a risky option (gamble) and a safe alternative. The risky options consisted of a 50% gain of either a larger or a smaller option. The safe options consisted of a 100% gain of an intermediate amount. To equate visual stimulation between the safe and the risky options, 2 times the same number was displayed for the safe option. Participants had to indicate their choice by button press during the 4-s presentation. After choice, the chosen option was framed for 0.5 s. No outcome was shown. Intertrial intervals consisted of a fixed part of 2 s and a variable with a high tail and a mean of 2 s [56]. At the end of the experiment, one trial was chosen randomly and played out to determine participants' payoff in Euro. There were four different risky options (gambles) presented (€15/€45, €10/€50, €40/€80, €30/€90), resulting in 2 levels of expected value, 30 and 60€, with the first one offering €15/€45 or €10/€50 gamble and the second one offering €40/€80 or €30/€90 gamble, respectively. There were 20 trials per gamble, with the safe option varied within the range of the risky option it was presented with. Specifically, according to precious studies [39,40], to ensure that the risky and safe alternatives have approximately the same utility, the safe option was defined by considering the risk variance and individuals' subjective expected value (see Fig 1B and the Methods

section of Supplementary Materials). The experiment comprised four sessions each consisting of 20 trials.

Blood Samples Acquisition

Twenty-two plasma amino acids as well as leptin and ghrelin were determined from blood samples drawn at 0830, 1000, 1130, and 1315 hours. From the blood samples drawn at 0830, 0900, 0915, 0930, 1000, 1030, 1130, and 1315 hours, the following parameters were determined: glucose, insulin, and cortisol. All the blood samples were centrifuged at 4 °C and stored at -80 °C until analysis. Blood glucose was measured by an enzymatic-amperometric method (EKF Diagnostic, Barleben, Germany). Insulin and cortisol were assessed by immunoassays (Immulite 2000, Siemens Healthcare Diagnostics, Erlangen, Deutschland). Leptin as well as active ghrelin concentrations were assessed by a radioimmunoassays (RIA Kit, EMD Millipore Corporation, St. Louis, Missouri, USA). Measurement of plasma amino acids was performed according to the method of Harder and colleagues [57]. Harder and colleagues combine precipitation, derivatization, and chromatographic separation to determine all proteinogenic amino acids, citrulline, and ornithine.

fMRI Data Acquisition

The imaging was performed on a 3T MRI system (Siemens Magnetom Skyra, Germany) using a 64-channel head-coil. Gradient echo-planar images (EPI) with 58 slices (voxel size: $3 \times 3 \times 3$ mm^3, field of view: 192 mm, 2000 ms repetition time

(TR), 30 ms echo time (TE), no distance factor) were acquired parallel to the commissural line (AC-PC) with the interleaved manner.

Statistical analyses

The rate of risk choices and response times were analyzed using t-tests and ANOVAs. In each trial, participant's subjective value for each value-risk domains were defined by fitting individual's choice responses according to equation 1.

$$\mathrm{SV(x)} = \beta_0 + \beta_1 \times EV_x + \beta_2 \times RV_x + \beta_3 \times Mag_x + \beta_4 \times EV_x \times RV_x + \varepsilon \qquad (1)$$

SV(x) is the subjective value of trial *x*, EV_x is the expected value of the risk option in trial *x*, RV_x is the risk variance of trial *x*, Mag_x is the net value of the safe option in trial *x*. According to the observation/findings in value-based risk decision making [39,40], we add interaction term to estimates the interactive effects between EV and variance on participants' subjective value. The betas (β) represent the participant-specific regression weights for the constant, benefit, risk cost, and the interaction. We also assumed that the probability of taking the risk option is given by a binary logistic regression [58] as follows:

$$P = \frac{1}{1+\exp(-\mathrm{SV})} \qquad (2)$$

By using the equation 1 and 2, we determined individual risk attitude for each risk option, which was defined as the point at which participants were indifferent between the risky and the safe option (indifferent point, IP).

Estimating risk-aversion. The identification of four individual IPs (two value levels × two risk levels) enabled us to compute the individual risk-aversion as the difference

between the IPs of two decision lotteries with the same EV ($IP_{low\ risk\ trial}$ - $IP_{high\ risk\ trial}$). In other words, more risk-prone individuals perceive the increase in risk as less important compared with more risk-aversive ones [39]. Mixed effects logistic regressions were carried out in MATLAB. We regressed participants' risk-aversion against nutrient-session and fat mass using a mixed effects logistic regression that included both fixed and random effects. All behavioral data analyses were performed by using MATLAB or SPSS. For the mediation effect, a bootstrapping test was conducted for the statistical significance using the mediation toolbox [25,26].

Metabolic parameters analysis

The influence of breakfast's macronutrient composition on plasma tryptophan, tyrosine and glucose levels was examined. Ratios between plasma concentrations of tryptophan and tyrosine and the other LNAAs were used as a proxy for brain tryptophan and tyrosine levels and ultimately brain serotonin and dopamine levels [1]. To dynamically track the nutrient-driven metabolic parameters changes, repeated-measures ANOVA was conducted with the time (0830-1315 hours) and session (high-carb/protein, low-carb/protein) as within-subject factors and tryptophan- or tyrosine/LNAA ratios and glucose levels as the dependent variable. Post-hoc tests were performed to investigate the exact relationship between sessions. Next, a paired t test was conducted to test for differences in glucose increase between 0830 and 0915 hours (see the results section of Supplementary Materials). Differences in AUC values (0830-1315 hours) of tryptophan- or tyrosine/LNAA ratios and glucose levels were

tested using paired t-tests (two-sided) (see the results section of Supplementary Materials).

Imaging data analysis

Spatial processing, subject-level modeling, and group-level statistics were conducted using Statistical Parametric Mapping (SPM12; Functional Imaging Laboratory, London, U.K.). The functional imaging data was spatially realigned, inspected for excessive motion (scans with displacement ≥ 3.0 mm were excluded), normalized to the standard Montreal Neurological Institute EPI template (voxel size = 3 × 3 × 3 mm^3), and smoothed with an isometric Gaussian kernel (full width at half-maximum of 5 mm). Subject-level models included onsets and durations of events convolved with the hemodynamic response function and motion parameters from realignment, and models were high-pass filtered at 128 s.

Statistical analysis of individual participant imaging data was performed using a general linear model (GLM) of BOLD responses [59]. The GLM was estimated to investigate macronutrient modulated risk processing depending on participants' choice responses. The GLM had 4 regressors: (1) indicator for safe choice trials in low risk condition, (2) indicator for safe choice trials in high risk condition, (3) indicator for gamble choice trials in low risk condition, (4) indicator for gamble choice trials in high risk condition. For this GLM, we calculated the following first-level single-subject contrasts: C1, the overall risk-processing by using the gamble trials minus safe choice trials across risk levels; C2, risk-processing in

risk-taking (gamble) trials between high and low risk levels; C3, risk-processing in safe choice trials between high and low risk levels.

A fixed effect model was used to create cross-run contrasts for each subject for a set of contrast images. These contrast images were entered into a second-level random-effects analysis using a paired t-test design to investigate between-condition effects (high- versus low-carb/protein conditions). Whole-brain statistical maps were voxel-level thresholded at $P < 0.005$ prior to undergoing cluster-level family-wise-error (FWE) correction ($P_{FWE} < 0.05$). The results were visualized using DPABI (http://rfmri.org/dpabi). All reported coordinates (x, y, z) are in MNI space.

To investigate the links between tryptophan metabolism, body fat mass and brain responses for gambling, the individual contrast images for high-carb/protein versus low-carb/protein sessions in gamble trials (C2) were made and used in the whole-brain regression analyses to assess its correlations with tryptophan/LNAA fluctuation and fat mass. Moreover, to investigate the convergence of tryptophan involved and fat mass predicted brain regions involved in risk-processing, a conjunction analysis was conducted between the two regression results. For conjunction analysis, we set the threshold of voxel level $P < 0.005$, $k > 20$ voxels for both images.

In the regression analyses, the front-parietal regions were identified as a function of risk-processing modulated by both tryptophan/LNAA fluctuation and body fat. Therefore, we preformed regression analysis extracting signals from the front-parietal conjunction regions to predict individual's risk-preference shift between the two

sessions (high- versus low-carb/protein).

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Author contributions

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Project administration: Soyoung Q. Park.

Supervision: Soyoung Q. Park.

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Competing interests

The authors declare no competing interests.

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Figure legends

Fig 1. Study design. (A) Timeline of the study. Subjects attended the research unit at 0730 hours and were prepared for the experiments. At 0845 hours subjects received breakfast according to the respective experimental condition. Blood was drawn at 8 time points. T1–T4 indicates blood samples used for measurement of tryptophan and tyrosine. (B) The risk decision making task procedure.

Fig 2. Nutrient manipulation on postprandial tryptophan/LNAA and glucose levels. Macronutrient composition-dependent changes in postprandial tryptophan/LNAA and glucose (mmol/L) levels. Red lines indicate high-carb/protein session and blue lines indicate low-carb/protein session for (A) tryptophan/LNAA ratio; (B) glucose concentrations (±SEM in shadowed area). High C/P, high-carb/protein breakfast; Low C/P, low-carb/protein breakfast; Tryp/LNAA, tryptophan/LNAA ratio. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

Fig 3. The body fat mass moderates effect of tryptophan fluctuation on risk-preference. (A) Individual fat mass measurements plotted against high- vs low-carb/protein breakfasts effect on tryptophan/LNAA fluctuation. (B) The prediction of tryptophan/LNAA fluctuation on nutrient-driven changes in risk-preference. (C) The prediction of individual fat mass on nutrient-driven changes in risk-preference. (D) Mediation Effect. The fat mass fully mediated the influence of △tryptophan/LNAA ratio on the nutrient-driven changes in risk-preference. Path coefficients are shown

next to arrows with standard errors in parentheses. The direct path c' is calculated controlling for the mediator. A bootstrapping test was conducted for the statistical significance of the product "a × b". Coefficients and p values were calculated using MATLAB. * $P < 0.05$, ** $P < 0.01$.

Fig 4. The brain-physiology relationship between metabolism, body composition and brain response. (A) Positive correlations between meal-induced tryptophan/LNAA fluctuation and high-carb/protein enhanced activation in the inferior parietal lobule (IPL) in response to risk-processing (in red); Positive correlations between individuals' body fat mass and brain activation during risk-processing in the IPL (in blue); The conjunction area is in yellow. (B) Scatterplots of correlation between tryptophan/LNAA metabolism changes and parameter estimates of the left IPL in risk-processing. (C) Scatterplots of correlation between fat mass and parameter estimates of the left IPL in risk-processing. All activations were thresholded using whole brain family-wise error (FWE) corrected ($P_{FWE} < 0.05$).

Fig 5. The front-parietal network is modulated by tryptophan fluctuation and fat mass and predicted individual's risk-shift. (A-C) Conjunction analysis identified the same regions in the front-parietal network, the high-carb/protein (vs low-carb/protein) increased activities of which associated with both tryptophan/LNAA fluctuation and fat mass. All activations were thresholded at voxel

level $P < 0.005$ and cluster size > 20. (D-F) The signals extracted from the front-parietal conjunction regions predicted the risk-preference shift. Scatterplots of correlations between parameter estimates of the IPL, dlPFC and OFC and nutrient-modulated risk-shift behavior during the risk decision-making.

References

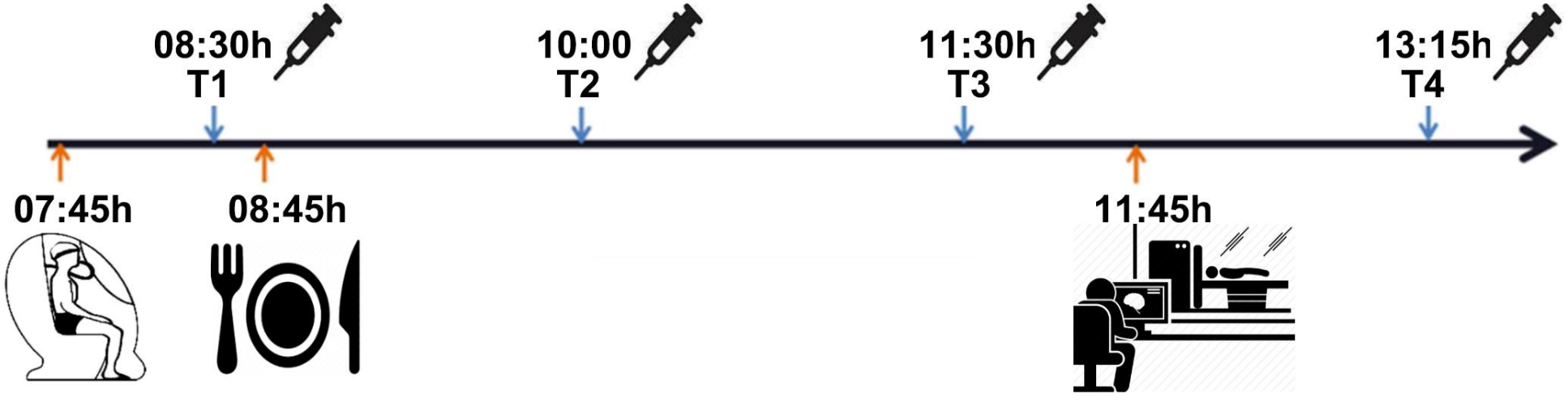
1. Wurtman RJ, Wurtman JJ, Regan MM, McDermott JM, Tsay RH, et al. Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. Am J Clin Nutr. 2003; 77: 128-132.
2. Fernstrom JD. Dietary effects on brain serotonin synthesis: relationship to appetite regulation. Am J Clin Nutr. 1985; 42: 1072-1082.
3. Fernstrom JD, Wurtman R. Brain serotonin content: physiological dependence on plasma tryptophan levels. Science 1971; 173: 149-152.
4. Strang S, Hoeber C, Uhl O, Koletzko B, Münte TF, et al. (2017) Impact of nutrition on social decision making. Proc Natl Acad Sci U S A. 2017; 114: 6510-6514.
5. Crockett MJ, Siegel JZ, Kurth-Nelson Z, Ousdal OT, Story G, et al. Dissociable effects of serotonin and dopamine on the valuation of harm in moral decision making. Curr Biol. 2015; 25: 1852-1859.
6. Namkung J, Kim H, Park S. Peripheral serotonin: a new player in systemic energy homeostasis. Mol Cells. 2015; 38: 1023.
7. Smeets PA, Charbonnier L, van Meer F, van der Laan LN, Spetter MS. Food-induced brain responses and eating behaviour. Proc Nutr Soc. 2012; 71: 511-520.
8. Lam DD, Garfield AS, Marston OJ, Shaw J, Heisler LK. Brain serotonin system in the coordination of food intake and body weight. Pharmacol Biochem Behav. 2010; 97: 84-91.
9. Oh C-M, Namkung J, Go Y, Shong KE, Kim K, et al. Regulation of systemic energy homeostasis by serotonin in adipose tissues. Nat Commun. 2015; 6: 6794.
10. Haub S, Ritze Y, Ladel I, Saum K, Hubert A, et al. Serotonin receptor type 3 antagonists improve obesity-associated fatty liver disease in mice. J Pharmacol Exp Ther. 2011; 339: 790-798.
11. Faulkner P, Deakin JW. The role of serotonin in reward, punishment and behavioural inhibition in humans: insights from studies with acute tryptophan depletion. Neurosci Biobehav Rev. 2014; 46: 365-378.
12. Homberg JR. Serotonin and decision making processes. Neurosci Biobehav Rev. 2012; 36: 218-236.
13. Crockett MJ, Clark L, Apergis-Schoute AM, Morein-Zamir S, Robbins TW. Serotonin modulates the effects of Pavlovian aversive predictions on response vigor. Neuropsychopharmacology. 2012; 37: 2244.
14. Geurts DE, Huys QJ, den Ouden HE, Cools R. Serotonin and aversive Pavlovian control of

instrumental behavior in humans. J Neurosci. 2013; 33: 18932-18939.
15. Crockett MJ, Clark L, Robbins TW. Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. J Neurosci. 2009; 29: 11993-11999.
16. Koot S, Zoratto F, Cassano T, Colangeli R, Laviola G, et al. Compromised decision-making and increased gambling proneness following dietary serotonin depletion in rats. Neuropharmacology. 2012; 62: 1640-1650.
17. Long AB, Kuhn CM, Platt ML. Serotonin shapes risky decision making in monkeys. Soc Cogn Affect Neurosci. 2009; 4: 346-356.
18. Rogers RD, Everitt B, Baldacchino A, Blackshaw A, Swainson R, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology. 1999; 20: 322-339.
19. Campbell-Meiklejohn D, Wakeley J, Herbert V, Cook J, Scollo P, et al. Serotonin and dopamine play complementary roles in gambling to recover losses. Neuropsychopharmacology. 2011; 36: 402.
20. Murphy SE, Longhitano C, Ayres RE, Cowen PJ, Harmer CJ, et al. The role of serotonin in nonnormative risky choice: the effects of tryptophan supplements on the “reflection effect” in healthy adult volunteers. J Cogn Neurosci. 2009; 21: 1709-1719.
21. Bateson M. Recent advances in our understanding of risk-sensitive foraging preferences. Proc Nutr Soc. 2002; 61: 509-516.
22. Gilby IC, Wrangham RW. Risk-prone hunting by chimpanzees (Pan troglodytes schweinfurthii) increases during periods of high diet quality. Behav Ecol Sociobiol. 2007; 61: 1771-1779.
23. Symmonds M, Emmanuel JJ, Drew ME, Batterham RL, Dolan RJ (2010) Metabolic state alters economic decision making under risk in humans. PLoS ONE. 2010; 5: e11090.
24. Fadda F. Tryptophan-free diets: a physiological tool to study brain serotonin function. Physiology. 2000; 15: 260-264.
25. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron. 2008; 59: 1037-1050.
26. Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL, et al. Brain mediators of cardiovascular responses to social threat: part I: reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. Neuroimage. 2009; 47: 821-835.
27. Gessa G, Biggio G, Fadda F, Corsini GU, Tagliamonte A. Tryptophan-free diet: a new means for rapidly decreasing brain tryptophan content and serotonin synthesis. Acta Vitaminol Enzymol. 1975; 29: 72-78.
28. Caballero B, Finer N, Wurtman RJ. Plasma amino acids and insulin levels in obesity: response to carbohydrate intake and tryptophan supplements. Metabolism. 1988; 37: 672-676.
29. Crockett MJ, Clark L, Smillie L, Robbins TW. The effects of acute tryptophan depletion on costly information sampling: impulsivity or aversive processing? Psychopharmacology. 2012; 219: 587-597.
30. He Q, Xue G, Chen C, Lu Z, Dong Q, et al. Serotonin transporter gene-linked polymorphic region (5-HTTLPR) influences decision making under ambiguity and risk in a large Chinese sample. Neuropharmacology. 2010; 59: 518-526.
31. Anderson IM, Richell RA, Bradshaw CM. The effect of acute tryptophan depletion on probabilistic

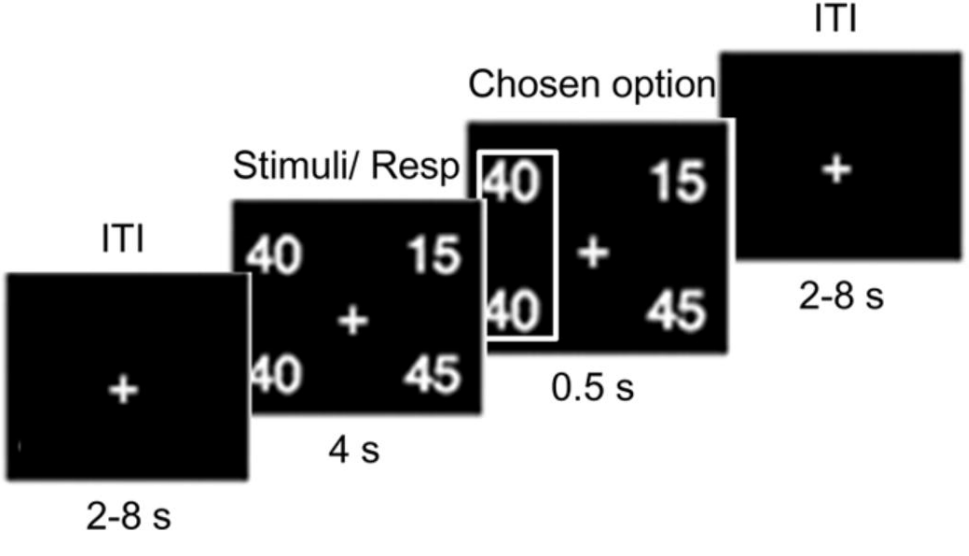
choice. J Psychopharmacol. 2003; 17: 3-7.
32. Macoveanu J, Fisher PM, Haahr ME, Frokjaer VG, Knudsen GM, et al. Effects of selective serotonin reuptake inhibition on neural activity related to risky decisions and monetary rewards in healthy males. Neuroimage. 2014; 99: 434-442.
33. Talbot PS, Watson DR, Barrett SL, Cooper SJ. Rapid tryptophan depletion improves decision-making cognition in healthy humans without affecting reversal learning or set shifting. Neuropsychopharmacology. 2006; 31: 1519.
34. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci. 2008; 12: 31-40.
35. Van Donkelaar E, Blokland A, Ferrington L, Kelly P, Steinbusch H, et al. Mechanism of acute tryptophan depletion: is it only serotonin? Mol Neuropsychiatry. 2011; 16: 695.
36. Krain AL, Wilson AM, Arbuckle R, Castellanos FX, Milham MP. Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. Neuroimage. 2006; 32: 477-484.
37. Studer B, Manes F, Humphreys G, Robbins TW, Clark L. Risk-sensitive decision-making in patients with posterior parietal and ventromedial prefrontal cortex injury. Cereb Cortex. 2013; 25: 1-9.
38. Platt ML, Huettel SA. Risky business: the neuroeconomics of decision making under uncertainty. Nat Neurosci. 2008; 11: 398-403.
39. Christopoulos GI, Tobler PN, Bossaerts P, Dolan RJ, Schultz W. Neural correlates of value, risk, and risk aversion contributing to decision making under risk. J Neurosci. 2009; 29: 12574-12583.
40. Tobler PN, Christopoulos GI, O'Doherty JP, Dolan RJ, Schultz W. Risk-dependent reward value signal in human prefrontal cortex. Proc Natl Acad Sci U S A. 2009; 106: 7185-7190.
41. Ishii H, Ohara S, Tobler PN, Tsutsui K-I, Iijima T. Dopaminergic and serotonergic modulation of anterior insular and orbitofrontal cortex function in risky decision making. Neurosci Res. 2015; 92: 53-61.
42. Macoveanu J, Rowe JB, Hornboll B, Elliott R, Paulson OB, et al. Serotonin 2A receptors contribute to the regulation of risk-averse decisions. Neuroimage. 2013; 83: 35-44.
43. Tanaka SC, Schweighofer N, Asahi S, Shishida K, Okamoto Y, et al. Serotonin differentially regulates short-and long-term prediction of rewards in the ventral and dorsal striatum. PloS ONE. 2007; 2: e1333.
44. Völlm B, Richardson P, McKie S, Reniers R, Elliott R, et al. Neuronal correlates and serotonergic modulation of behavioural inhibition and reward in healthy and antisocial individuals. J Psychiatr Res. 2010; 44: 123-131.
45. Völlm B, Richardson P, McKie S, Elliott R, Deakin J, et al. Serotonergic modulation of neuronal responses to behavioural inhibition and reinforcing stimuli: an fMRI study in healthy volunteers. Eur J Neurosci. 2006; 23: 552-560.
46. Erritzoe D, Frokjaer VG, Haugbol S, Marner L, Svarer C, et al. Brain serotonin 2A receptor binding: relations to body mass index, tobacco and alcohol use. Neuroimage. 2009; 46: 23-30.
47. Erritzoe D, Frokjaer VG, Haahr MT, Kalbitzer J, Svarer C, et al. Cerebral serotonin transporter binding is inversely related to body mass index. Neuroimage. 2010; 52: 284-289.
48. Haahr ME, Rasmussen PM, Madsen K, Marner L, Ratner C, et al. Obesity is associated with high serotonin 4 receptor availability in the brain reward circuitry. Neuroimage. 2012; 61: 884-888.
49. Hesse S, Rullmann M, Luthardt J, Winter K, Hankir MK, et al. Central serotonin transporter availability in highly obese individuals compared with non-obese controls: A [11 C] DASB positron

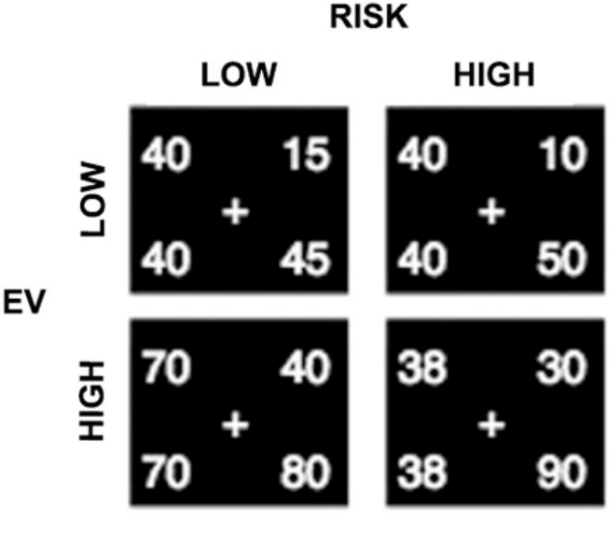
emission tomography study. Eur J Nucl Med Mol Imaging. 2016; 43: 1096-1104.
50. Breum L, Rasmussen MH, Hilsted J, Fernstrom JD. Twenty-four–hour plasma tryptophan concentrations and ratios are below normal in obese subjects and are not normalized by substantial weight reduction. Am J Clin Nutr. 2003; 77: 1112-1118.
51. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009; 9: 311-326.
52. Crandall EA, Fernstrom JD. Acute changes in brain tryptophan and serotonin after carbohydrate or protein ingestion by diabetic rats. Diabetes. 1980; 29: 460-466.
53. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988; 54: 1063.
54. Rammstedt, B, John, OP. Measuring personality in one minute or less: A 10-item short version of the Big Five Inventory in English and German. J Res Pers. 2007; 41, 203-212.
55. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol. 1994; 67: 319.
56. Hagberg GE, Zito G, Patria F, Sanes JN. Improved detection of event-related functional MRI signals using probability functions. Neuroimage. 2001; 14: 1193-1205.
57. Harder U, Koletzko B, Peissner W. Quantification of 22 plasma amino acids combining derivatization and ion-pair LC–MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2011; 879: 495-504.
58. Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression. John Wiley & Sons; 2013.
59. Friston KJ, Holmes AP, Poline J, Grasby P, Williams S, et al. Analysis of fMRI time-series revisited. Neuroimage. 1995; 2: 45-53.

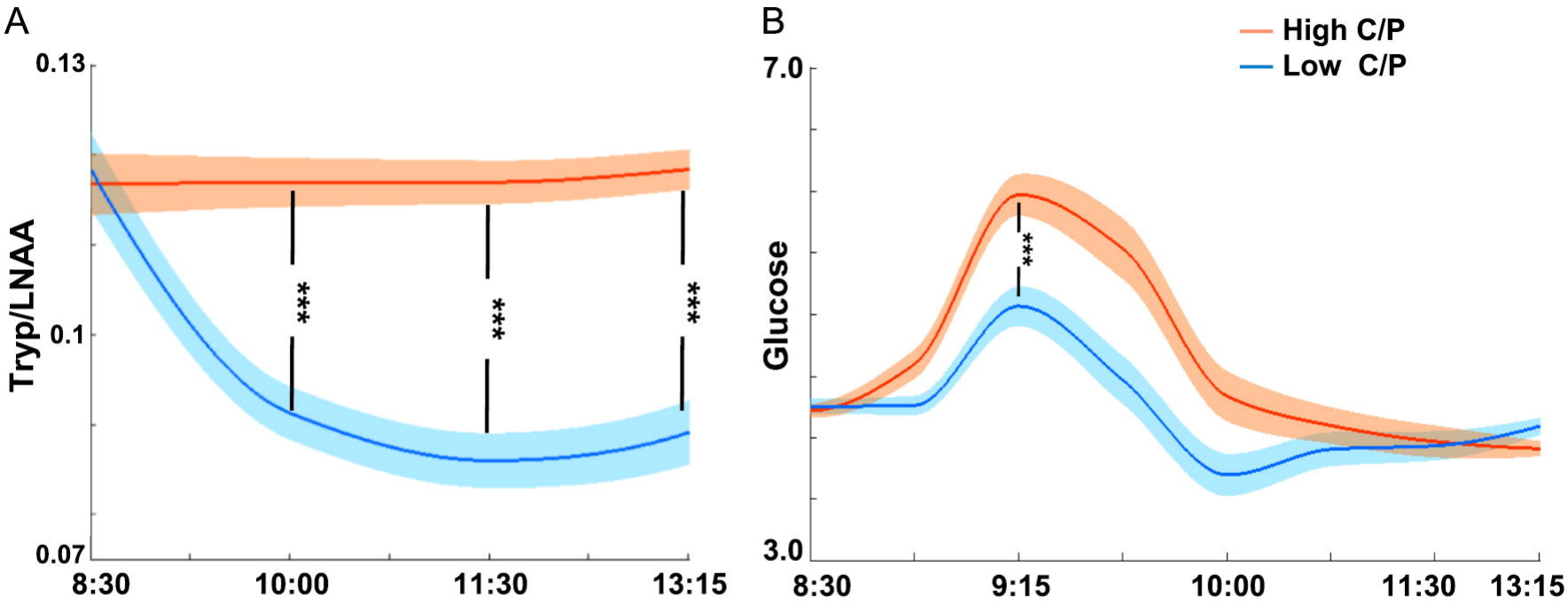
A Timeline of the study

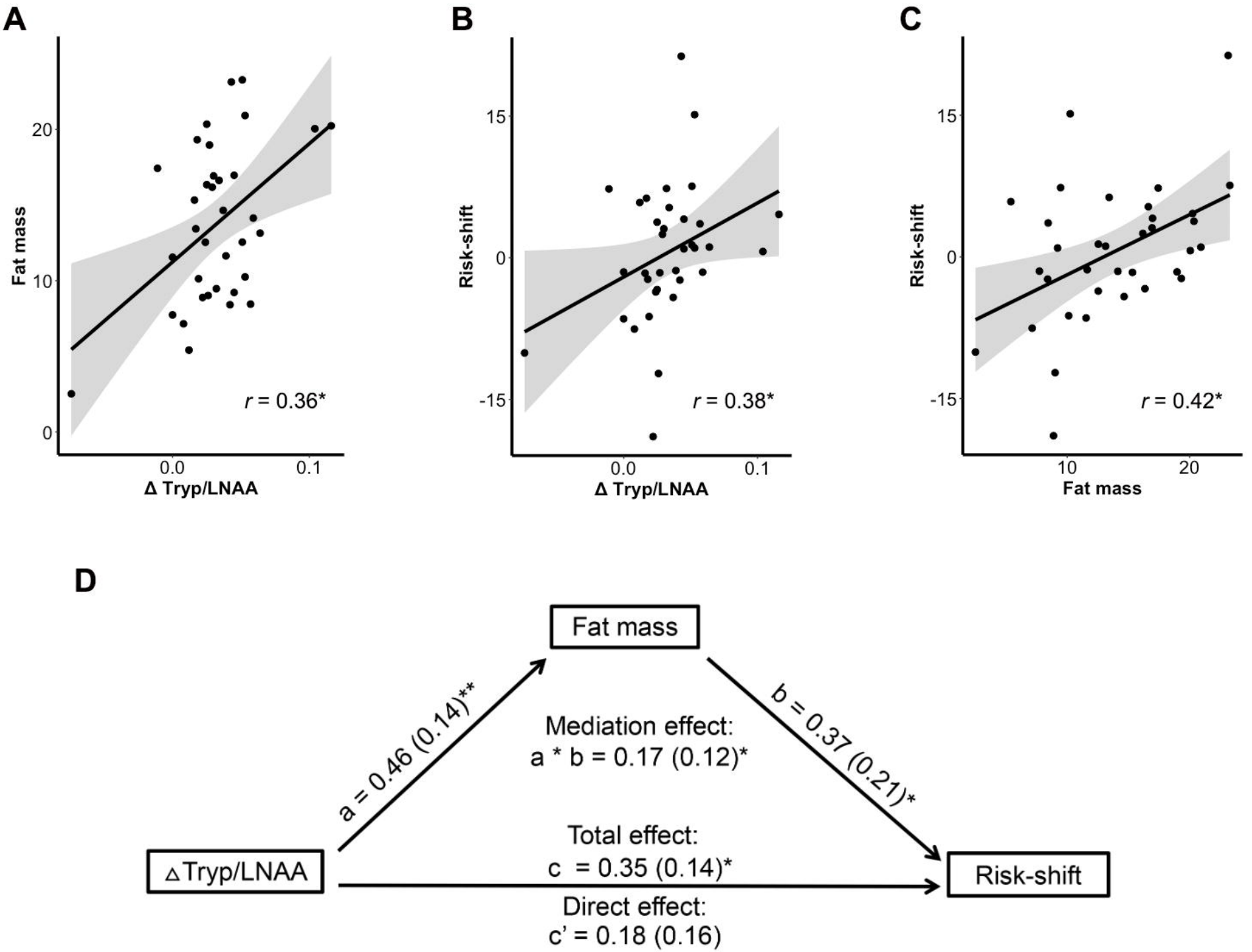


B Risk decision-making task






A
0.13
0.1
0.07
Tryp/LNAA
***
***
***
8:30
10:00
11:30
13:15
B
High C/P
Low C/P
7.0
3.0
Glucose
***
8:30
9:15
10:00
11:30
13:15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Fat mass
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0
0.0
0.1
Δ Tryp/LNAA
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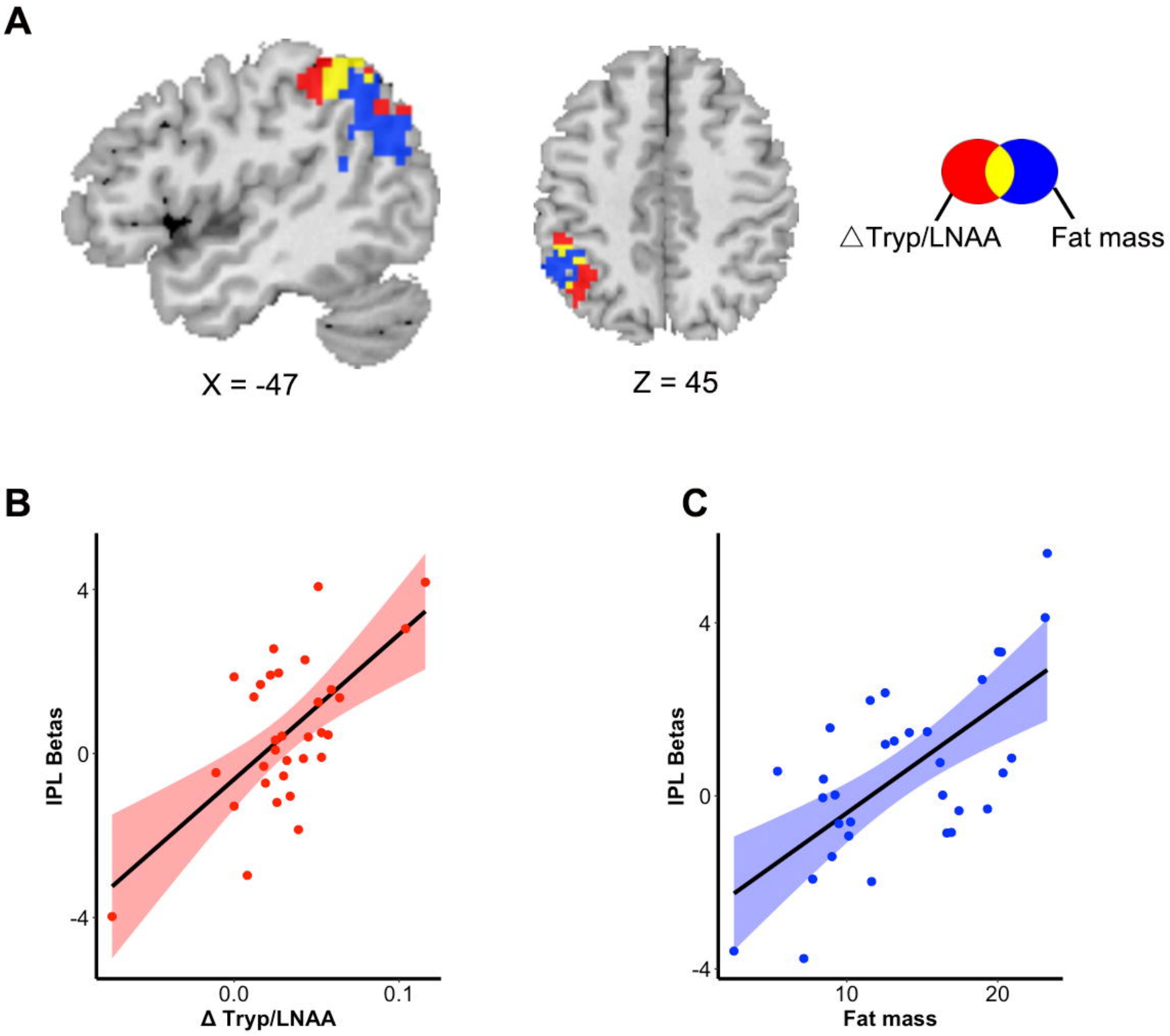
B
Risk-shift
15
0
-15
0.0
0.1
Δ Tryp/LNAA
r = 0.38*
C
Risk-shift
15
0
-15
10
20
Fat mass
r = 0.42*
D
Fat mass
a = 0.46 (0.14)**
b = 0.37 (0.21)*
Mediation effect:
a * b = 0.17 (0.12)*
Total effect:
c = 0.35 (0.14)*
Direct effect:
c' = 0.18 (0.16)
△Tryp/LNAA
Risk-shift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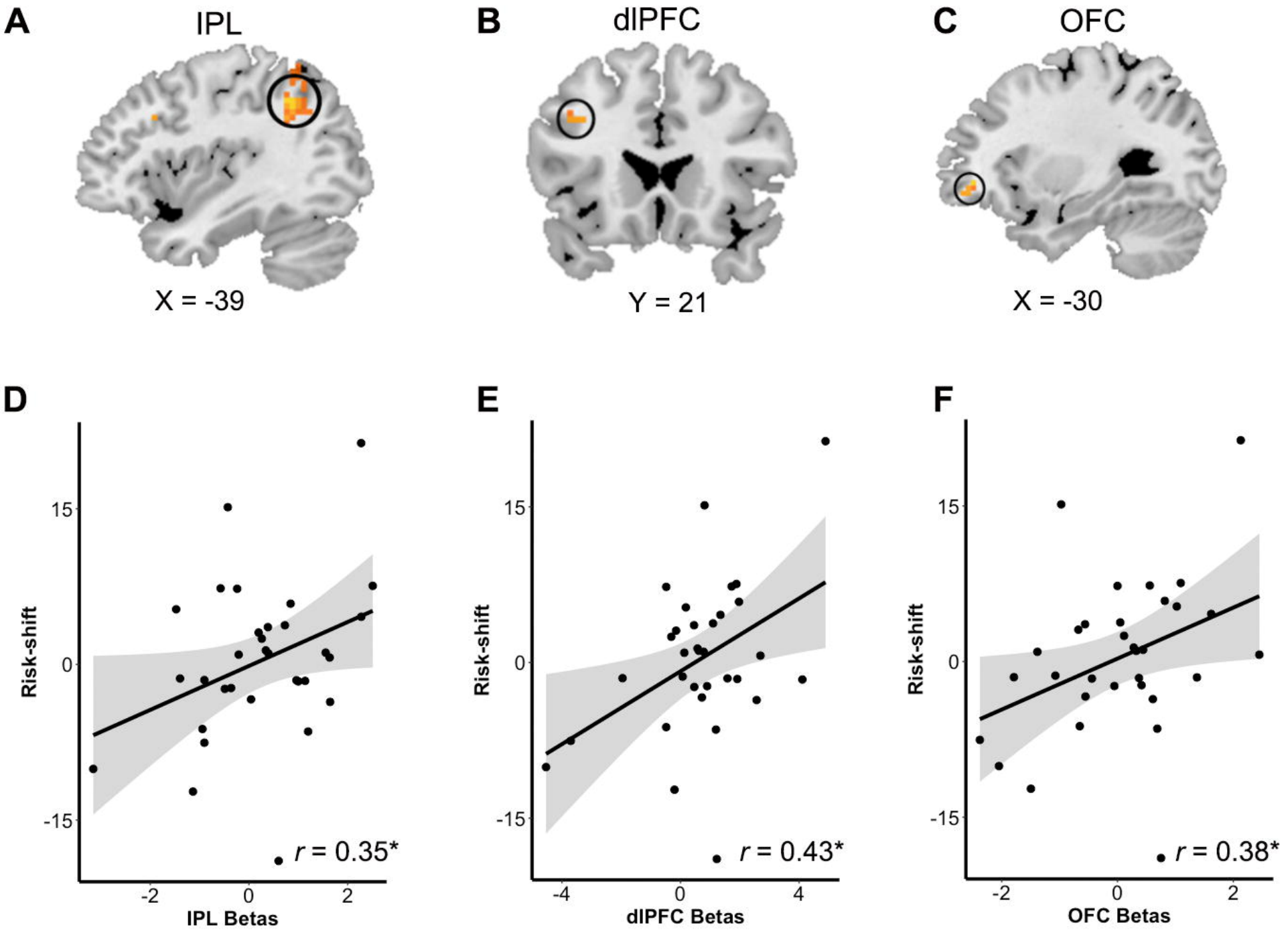
Δ Tryp/LNAA
C
IPL Betas
4
0
-4
10
20
Fat mass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C
OFC
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D
E
F
Risk-shift
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-15
-2
0
2
IPL Betas
r = 0.35*
-4
4
dlPFC Betas
r = 0.43*
OFC Betas
r = 0.38*