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Research Paper

Plasma LEAP2 concentration is associated with attention and cognitive responses to low-calorie food cues in men depending on body weight status

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ABSTRACT

Background: The putative role of LEAP2 in central nervous system functions such as attentional or cognitive processes related to food intake remain poorly understood in humans.
Aims: To investigate the relationship between fasting LEAP2 concentration and attentional or cognitive processes related to food cues, and whether body weight status may modulate them.
Methods: Stroop-Food and Stroop Low-Calorie/High-Calorie food tasks, Attention-Network-Test, Iowa-Gambling-Task, and fasting LEAP2 concentration were assessed in 108 men aged 18–40 yr with normal weight (NW) and 91 with overweight or obesity (OW/OB). Multivariable linear regression analyses were conducted to examine the relationship between fasting LEAP2 concentration and behavioral tests outcomes.
Results: Individuals with OW/OB exhibited lower number of correctly identified words in the Stroop Food and Stroop Low-Calorie/High-Calorie Food tasks and had higher LEAP2 concentrations compared to NW participants ($p < 0.01$). Fasting LEAP2 was positively associated with Executive attention [Beta (95 % CI): 21.18 (2.91, 39.45), $p = 0.024$], and inversely with Alerting attention [Beta (95 % CI):18.04 (-35.52, -0.57), $p = 0.043$], in NW but not in subjects with OW/OB. LEAP2 was positively related with responses to low-calorie food words [Beta (95 % CI): 11.88 (0.52, 23.25), $p = 0.041$] only in subjects with OW/OB.
Conclusion: LEAP2 is associated with attention and cognitive responses in men depending on body weight status. It may play a differential role in cognitive processes related to food intake, particularly in individuals with OW/OB while influencing attentional processes in lean subjects.
Clinical Trial Registry: This study was registered at clinicaltrials.gov as NCT01863212. https://clinicaltrials.gov/study/NCT01863212

1. Introduction

Liver-enriched antimicrobial peptide 2 (LEAP2) was identified in 2018 as an endogenous inhibitor of the growth hormone secretagogue receptor (GHSR), which binds the hormone ghrelin [1–5]. Circulating LEAP2 acts in opposition to ghrelin, decreasing during energy deficits and increasing after refeeding in mice [1,6]. Plasma LEAP2 levels have been observed to rise in individuals with obesity [7,8], consistent with findings in mice [1,7]. Positive correlations between LEAP2, adiposity, body mass index (BMI), and glycemia have been documented in individuals with normal weight (NW), overweight (OW), or obesity (OB) [7,8]. Further, recent data from a large cohort show stronger

Abbreviations: ANT, Attention Network Test; BMI, body mass index; CI, confidence interval; GHSR, growth hormone secretagogue receptor; IGT, Iowa Gambling Task; IQR, interquartile range; HC, high-calorie; LC, low-calorie; LEAP2, liver-enriched antimicrobial peptide 2; NW, normal weight; OB, obesity; OW, overweight.

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associations between plasma LEAP2 and anthropometric measures in subjects with OB compared with NW [9], while LEAP2 relationship with glycemia is noted only in those of NW [9]. Thus, LEAP2 physiological effects appear to be dependent on body weight status.

LEAP2 infusion reduces ad libitum food intake in healthy men [10]. Furthermore, previous studies from our group [8,9] and others [11] underscored the significant role of endogenous LEAP2 in specific aspects of human eating behavior. Notably, we found that pre-prandial plasma LEAP2 concentrations are inversely correlated with hunger sensations [8] and reward responsiveness while showing a direct association with fullness [9]. Preprandial LEAP2 concentrations are inversely associated with caloric intake among individuals who do not completely consume a provided test meal, regardless of weight status [12]. LEAP2 concentration was also reported to be dysregulated in patients with anorexia nervosa, indicating a potential role in eating disorders [13]. Based on these findings, it is hypothesized that LEAP2 may also influence additional aspects of eating behavior, such as food perception, attentional focus on food stimuli, and cognitive control over food-related decisions. Understanding the neuroendocrine regulation of attention and cognition related to food could shed light on the biological mechanisms behind food choices, impulsive eating, and long-term dietary habits.

Despite increasing evidence for a specific role of LEAP2 in hunger and satiety regulation, its associations with higher central nervous system functions, such as attentional and cognitive processes related to food, remain largely unexplored. Specific cognitive processes relevant to eating behavior, such as attentional mechanisms and inhibitory control, can be evaluated using the Stroop Color–Word Task [14]. In this test, participants are shown color words printed in various ink colors and are asked to name the ink color rather than the word itself. Conflict arises when the word and ink color differ (e.g., the word "blue" in yellow ink), resulting in delayed or inaccurate responses. Slower responses are typically interpreted as indicators of attentional bias or cognitive interference, whereas response accuracy reflects cognitive control and the ability to inhibit distraction by salient stimuli [15]. To assess cognitive processes specific to food cues, the Stroop test has been adapted to include food-related words (Stroop Food Task) [16,17]. Increased interference with food-related words has been noted in subjects with obesity [18,19]. Attentional processes related to food involve how the brain allocates cognitive resources to detect, focus on, and respond to food stimuli.

Other cognitive processes relevant to eating behavior include selective attention, which comprises three neural networks: alerting, orienting, and executive control [20]. The alerting network maintains heightened sensitivity to incoming stimuli, the orienting network shifts attention to specific spatial locations, and the executive control network resolves conflicts among competing responses, especially in situations with conflicting information. These networks are distinctly assessed using the Attention Network Test (ANT) [20,21]. Attentional processes may be affected in obesity, as individuals with OW show greater attentional bias toward food cues [22]. Additionally, subjects with OB exhibit reduced executive attention and greater effortful control compared to those with NW [23]. Although cognitive impairments in OB have been investigated [18,19,23], the underlying mechanisms remain understudied. LEAP2 concentration has been linked to decision-making in patients with gambling disorder, as assessed by the Iowa Gambling Task (IGT) [24]. The IGT is a psychological test that assesses decision-making under uncertainty by having participants choose cards from four decks, each with varying rewards and penalties. Over time, individuals are expected to learn to favor decks that yield long-term gains, revealing their ability to balance short-term rewards against long-term outcomes [25]. Also, LEAP2 concentrations have been associated with impulsivity in OB subjects [9]. However, the implications of plasma LEAP2 on cognitive processes related to eating behavior and its potential modulation by body weight status remains unclear.

Here, we hypothesized that plasma LEAP2 concentration could be associated with attention, cognitive processes related to food and/or decision-making. We also hypothesize that these associations could be modulated by body weight status. This study investigates the relationship between fasting LEAP2 concentration and attentional or cognitive processes related to food cues, and whether body weight status modulates these associations. We analysed data and samples from a large cohort with a broad range of BMI values, collected from a study we previously described [9].

2. Methods

2.1. Study participants

Data and plasma samples for LEAP2 assessment in male individuals were obtained from a study conducted at Uppsala University between August 2011 and August 2018. This study recruited healthy volunteers with normal eating habits to study genetic and epigenetic effects on food intake, as previously described [9,26]. Between 08/2011 and 08/2018, participants were recruited from public university campuses in Uppsala. The participants included in this study were part of a project that recruited healthy volunteers to study genetic and epigenetics effects related to food intake, as previously described [26]. Inclusion criteria: healthy subjects aged 18–40 years with normal dietary habits and of northern ancestry (grandparents born in Sweden, Denmark, Norway, Finland, or Iceland). Exclusion criteria: vegetarians/vegans, smokers, lactose or gluten intolerant (**Supp Figure 1**). Only data and plasma samples from male participants with fasting LEAP2 measurements were included in this study ($n = 199$), as behavioral test outcomes from female participants were limited in number ($n = 85$, of which $n = 62$ had fasting LEAP2 measurements) and unevenly distributed across weight status categories ($n = 49$ NW and $n = 13$ OW/OB). Thus, 108 NW and 91 OW/OB men were considered eligible for the present cross-sectional analysis. Ethical approval was granted by the ethical review board (Uppsala). Informed consents were obtained. The study was carried out following the Declaration of Helsinki and registered in clinicaltrials.gov (NCT01863212).

2.2. Study protocol

The study design is depicted in Fig. 1A. Participants arrived at the Institute in the morning after a 12-h fast and underwent an initial evaluation, including medical and family history. Education level was assessed by recording years of formal education. Weight, height, and waist circumference were measured using standard procedures [27]. Participants were categorized into normal weight (NW; BMI 18.5–24.99 kg/m^2), and with overweight or obesity (OW/OB; BMI$\geq$25 kg/m^2) [28]. Next, a blood sample was obtained, and plasma samples were collected and stored at −80 °C until analysis. Participants were requested to perform the Stroop Food Task in the fasting state to ensure a comparable hunger state among participants, as previously suggested [17,29]. Half an hour later, participants received a breakfast test meal consisting of one piece of whole-grain bread (70 g, Fruktkuse, Coop Sverige AB) with 3 slices of Leerdamer cheese (60 g) and 250 g of Quark curd cheese (Arla, Sweden). The meal comprised 583.13 kcal, of which 205.36 kcal (35.33 kcal %) was protein, 182.79 kcal (31.33 kcal %) were total carbohydrates, and 194.98 kcal (33.33 kcal %) was fat. Water (30 mL) was provided as a beverage. Half an hour later, participants were requested to perform the Stroop low-calorie/high-calorie (LC/HC) food task, the ANT, and the IGT. To further explore the specificity of food-related words to affect cognitive control, the Stroop task comparing LC and HC food cues was administered following meal consumption, to minimize interindividual variability and better reflect a standardized postprandial state. This task enables the assessment of differential attentional bias toward energy-dense, palatable foods, providing insight into qualitative differences in cognitive processing based on food type. The ANT and IGT were conducted afterward for logistical reasons within the study protocol, as we found no literature indicating that the fasting

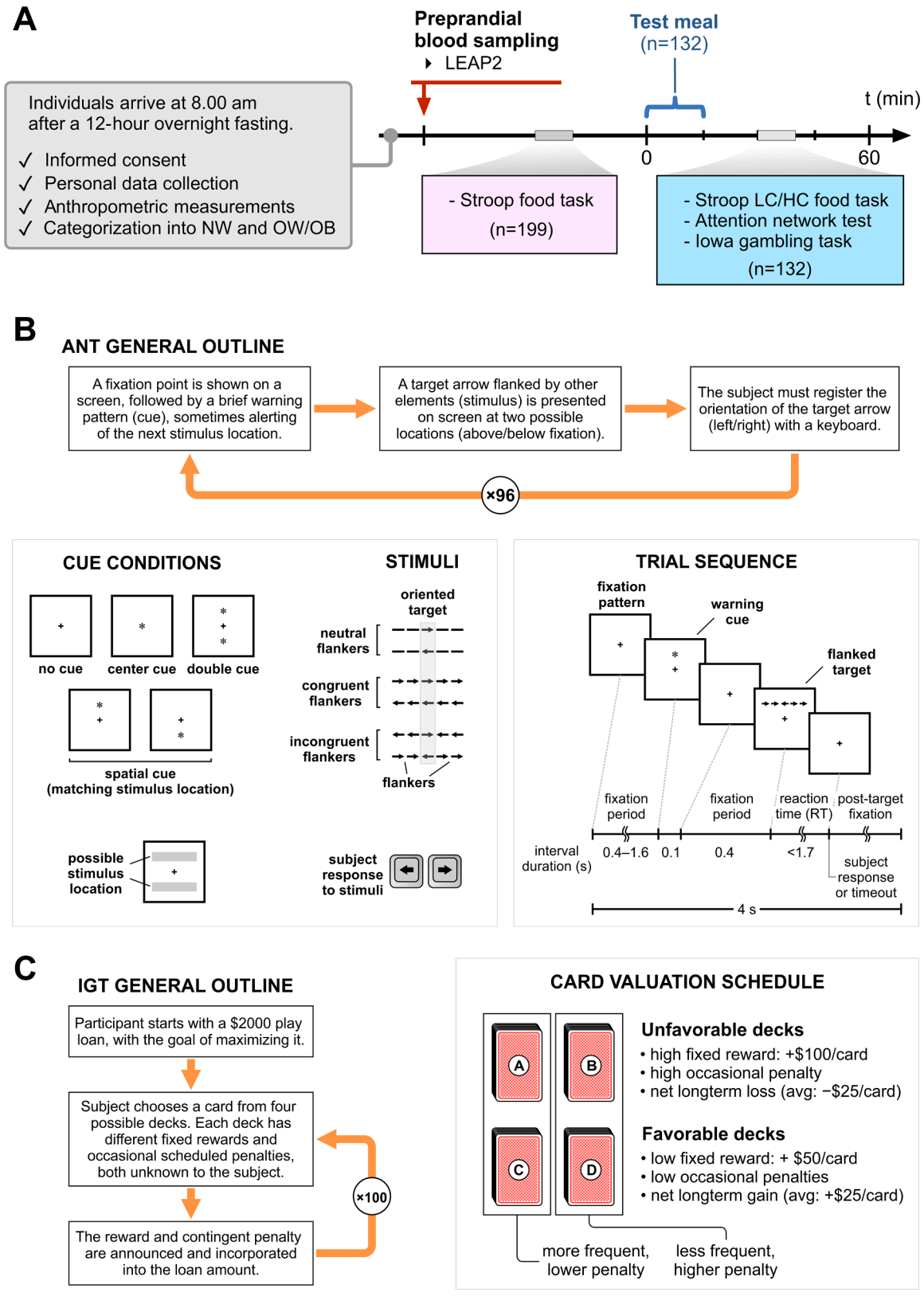

Fig. 1. A. overview of the study design. **B**. illustration of the experimental procedure for the Attention Network Test (ANT). **C**. illustration of the experimental procedure for the Iowa Gambling Task (IGT).

or fed state significantly affects their outcomes. Due to the complexity of the experimental protocol, each participant was tested individually on separate experimental days. Thus, no interaction occurred between participants at any time.

2.3. Behavioral tests

1- Stroop Food Task: cognitive control from food-related cues was measured using the Stroop colour-naming task, presenting neutral and

food-related words printed in different colors as in Hogenkamp et al. [29]. Each participant received two sheets of paper, each containing a block of 100 words: one block with neutral words (e.g., Swedish equivalents of "rain," "birch," "bee," "growing branch," "deer") and one with food-related words (e.g., Swedish equivalents of "salt," "ham," "chocolate," "orange," "rice," "cucumber"). In the food block, the counts of LC and HC were intermixed and evenly divided, with half of the words referring to LC foods and the other half to HC foods, mixed to avoid predictability and minimize response bias. Food items were selected based on typical dietary consumption patterns in Sweden. The order of the blocks was counterbalanced, as participants were previously randomized to read either neutral or food words first. Participants were instructed to name the color in which each word was printed from left to right as quickly as possible within 60 s, i.e. to inhibit the prepotent reading response. The design of the task mirrored that of the validated Color Stroop [14]. The performance in this test was assessed as the number of correctly identified (valid) words within 60 s, representing response accuracy.

2- Stroop LC/HC food task: Upon completion of the Stroop Food Task, participants completed a similar task but presenting blocks of 100 LC (e.g., Swedish equivalents of wheat, cauliflower, soy, milk) and 100 HC (e.g., Swedish equivalents of pizza, muffins, cream cake, pancake, bacon) food-related words printed in different colors. Rice, pear, orange, egg, carrot, cucumber, coffee and potato (LC words) as well as juice, sugar, steak, roll and chocolate (HC words) were used in both the Stroop Food and the Stroop LC/HC food tasks. The use of separate LC and HC word blocks to compare responses was adapted from Phelan et al. [17]. Our version differed in some aspects, including the use of some food-related words adapted to Swedish dietary habits and a 60-second response window, aligning more closely with the traditional Stroop format. The performance in this test was assessed as the number of correctly identified (valid) words within 60 s, representing response accuracy.

3- Attention Network Task (ANT): Efficiency of the three attentional networks (alerting, orienting and executive control) was assessed by measuring how response times (RTs) are influenced by alerting cues, spatial cues, and flankers (Fig. 1B) The task was carried out following the validated protocol established by Fan et al. [20,21] and presented on a laptop using Presentation (Version 9, Neurobehavioral Systems, Davis). Stimuli consisted of a row of five visually presented horizontal black lines, with arrowheads pointing leftward or rightward, against a grey background. The target was a leftward or rightward arrowhead at the center. This target was flanked on either side by two arrows in the same direction (congruent condition), or in the opposite direction (incongruent condition), or by lines (neutral condition). The participants' task was to identify the direction of the centrally presented arrow by pressing one key for the left direction and a different key for the right direction. Each trial consisted of five events: a fixation period of randomized length, a warning cue presentation, a short fixation period, and the target and flanker presentation. After participants made a response, the target and flankers disappeared immediately and there was a post target fixation period for a variable duration, which was adjusted based on the duration of the first fixation and RT so that each trial lasted 4 s in total. After this interval, the next trial began. The fixation cross appeared at the center of the screen during the whole trial. To introduce an attentional-**orienting** component to the task, the row of five stimuli was presented in one of two locations outside the point at which the subject was fixating. Target location was always uncertain except when spatial cue was presented. There were four warning conditions: no cue, center cue, double cue, and spatial cue. For the no-cue trials, participants saw only a fixation for 100 msec. Under this condition, there were neither alerting nor spatial cues. For the center-cue trials, participants were shown an asterisk at the location of fixation cross for 100 msec. Therefore, alerting was involved. For the double-cue trials, the time course was the same as in the center-cue trials except that there were two warning cues corresponding to the two possible target positions—up and down. It was expected that the alerting was involved but the attentional field was larger under the double-cue condition than under the central-cue condition. For the spatial-cue trials, the cue was at the target position and the time course was the same as in the center-cue and double-cue trials. The spatial cues were always valid, which means that they were displayed right on the locations of the targets. It was expected that both alerting and orienting were involved under this condition. The variable duration of the first fixation was used to produce additional uncertainty about cue onset. A session consisted of a 24-trial full-feedback practice block and three experimental blocks of trials with no feedback. Each experimental block consisted of 96 trials (4 cue conditions x 2 target locations x 2 target directions x 3 flanker conditions x 2 repetitions). The presentation of trials was in a random order. Participants were instructed to focus on a centrally located fixation cross throughout the task and to respond as quickly and accurately as possible. The **alerting** effect was calculated by subtracting the mean RT of the double-cue conditions from the mean RT of the no-cue conditions. Neither of these conditions provided information about whether the target stimulus would appear above or below the fixation point. When no warning cue is presented, attention tends to remain diffused across the two potential target locations. The double cue was used because it also tends to keep attention diffused between the two potential target locations, while alerting the participant to the imminent appearance of the target. The **orienting** effect was calculated by subtracting the mean RT of the spatial cue conditions from the mean RT of the center cue. Both center and spatial cues serve as a form of alerting cue, but only the spatial cue provides predictive spatial information that allows subjects to begin orienting attention to the appropriate location before the target arrives. The center cue was used as a control because, like the single cue, it encourages orienting attention to one location. The conflict (**executive** control) effect was calculated by subtracting the mean RT of all congruent flanking conditions, summed across cue types, from the mean RT of incongruent flanking conditions. The use of neutral, instead of congruent, flanking conditions would produce the same result because there were only small differences between the congruent flanker and the neutral flanker conditions [21].

4- Iowa gambling task (IGT): The IGT [25] is a computerized task for evaluating risk/reward-based and punishment-influenced decision--making (Fig. 1C). The participants were assigned a $2000 play money loan and told that the purpose of the task was to win as much money as possible. Participants had to pick a card from four decks of cards, labelled A, B, C, and D, and, after each card selection, either a monetary gain or a loss was obtained. This was repeated for a total of 100 cards (undisclosed beforehand to the subjects), divided into 5 equal blocks. Each deck was associated with fixed rewards, $50 for decks A and B and $25 for C and D, and occasionally pre-scheduled penalties such that cards from decks A or B resulted in a net loss of money ($25 on average). In contrast, decks C and D produced a net gain of money ($25 on average). Therefore, decks A and B had large apparent wins but also significant losses, ultimately making them disadvantageous, whereas decks C and D had small wins but small penalties, making the selection of these decks more optimal. Both decks of either net gain or net loss differed in the frequency and size of the penalties. The test was scored by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. The total task score (IGT-Total) was obtained by adding the scores of the five blocks. The learning score (IGT-Learning) measures the differences between the two first blocks (where the participant has not learned which decks are advantageous and disadvantageous) and the two last blocks (where the participant could have already detected which decks involve a risky choice and then, the experience gained through the trial can produce changes in choice patterns). Additionally, the risk score (IGT-Risk) was measured considering the scores from the two last blocks.

Table 1
Characteristics of the participants.

	All ($n = 199$)	NW ($n = 108$)	OW/OB ($n = 91$)	p-value
BMI (kg/m²) [a]	24.4 (22.3–26.8)	22.5 (21.4–23.8)	27.0 (25.7–29.4)	**<0.001**
Age (years) [a]	26 (23–28)	25.5 (23.0–27.7)	26 (23–28)	0.578
Education (years) [a]	15.5 (14–17)	16 (15–17)	15 (13–17)	0.399
LEAP2 (ng/ml) [b]	12.92 (12.19, 13.69)	11.98 (11.09, 12.95)	14.12 (12.95, 15.40)	**0.005**
Stroop Food Task				
Number of valid neutral words [a]	78 (66, 88)	81 (70, 90)	73.5 (63.7, 84.2)	**0.002**
Number of valid food words [a]	80 (69, 90)	84 (73, 93)	75.5 (62.7, 86.0)	**<0.001**
	($n = 132$)	**($n = 84$)**	**($n = 48$)**	
Stroop LC/HC food task				
Number of valid LC food words [a]	82.0 (71.0, 96.0)	85.0 (75.0, 97.0)	77.5 (66.5, 92.0)	**0.005**
Number of valid HC food words [a]	82.0 (70.0, 94.0)	84.0 (76.5, 94.5)	78.5 (64.2, 91.2)	**0.003**
ANT				
Orienting (ms) [c]	49.25 (34.02)	50.46 (35.83)	46.88 (30.40)	0.567
Alerting (ms) [c]	31.92 (40.49)	37.13 (34.59)	23.00 (48.03)	0.067
Executive (ms) [c]	100.49 (37.05)	98.68 (37.55)	103.76 (36.27)	0.443
IGT				
Total score [a]	100 (100, 101)	100 (99, 100)	100 (100, 102)	**0.014**
Learning score [a]	−10.5 (−32.2, 6.2)	−15 (−38, 9)	−6 (−26, 6)	0.274
Risk score [a]	56 (47, 67)	58 (46, 69)	54 (47, 63)	0.347

Values in bold represent statistical significance using Student or Mann–Whitney tests.
Abbreviations: NW: normal weight, OW/OB: overweight/obesity, LC: low calorie; HC: high calorie; ANT: attention network test, ms: miliseconds; IGT: Iowa gambling test.
[a] Data is presented as median (IQR).
[b] Data analysis performed on natural log-transformed values. Back-transformed values are presented as geometric means and 95 % confidence intervals.
[c] Data is presented as mean and standard deviation (SD).

2.4. Biochemical analyses

LEAP2 was assessed using an immunoassay from Phoenix Pharmaceutical (EK-075–40, intra- and inter-assay variations of 6.4 and 9.9 %, respectively, validated in [7].

2.5. Statistics and data analyses

Statistical analyses were performed using R software version 4.0.3 or SPSS Version 28.0. Variables with normal distributions were summarized as mean and standard deviation (SD), while non-normally distributed data were presented as median (interquartile range, IQR). LEAP2 concentration was log-transformed prior to analysis to account for positive skewness. Differences by BMI category were analyzed using Student's *t*-test or the Mann–Whitney test, as appropriate. Multivariable linear regression analyses were conducted to examine the relationship between fasting LEAP2 concentration (exposure) and behavioral test outcomes (dependent variables) with age, BMI and educational level adjustments. Interaction analyses were performed to determine if BMI (as a continuous variable) modified the association between LEAP2 concentration and the variables of interest; a BMI × LEAP2 interaction term was added to the adjusted model. If the interaction was significant, participants were analyzed separately based on their body weight status (NW vs. with OW/OB). The distribution of residuals was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov tests and normal quantile plots, and regression diagnostics were conducted to confirm that the assumptions of linear regression were met. Power calculations were omitted as data were derived from a pre-existing clinical trial.

Table 2
Associations between fasting LEAP2 concentration and behavioral tests outcomes.

	All		BMI x LEAP2 interaction	NW		OW/OB	
Plasma LEAP2 concentration (ng/mL)	Beta (95 % CI)	p	p	Beta (95 % CI)	p	Beta (95 % CI)	p
Stroop food task							
Number of valid neutral words [§]	1.55 (−3.10, 6.22)	0.511	0.561				
Number of valid food words [§]	2.32 (−3.09, 7.74)	0.399	0.570				
Stroop LC/HC							
Number of valid LC food words [§]	3.76 (−2.51, 10.04)	0.238	**0.043**	0.607 (−6.580, 7.800)	0.867	11.88 (0.52, 23.25)	**0.041**
Number of valid HC food words [§]	1.58 (−4.59, 7.77)	0.612	0.489				
ANT							
Orienting	0.85 (−13.62, 15.34)	0.907	0.635				
Alerting	−6.20 (−22.97, 10.55)	0.465	**0.028**	−18.04 (−35.52, −0.57)	**0.043**	20.15 (−13.12, 56.43)	0.270
Executive	9.61 (−5.84, 25.06)	0.221	**0.012**	21.18 (2.91, 39.45)	**0.024**	−7.74 (−37.51, 22.02)	0.603
IGT							
Total score [§]	3.70 (−8.15, 15.56)	0.538	0.476				
Learning score	0.98 (−13.19, 15.16)	0.891	0.341				
Risk score	−0.31 (−7.26, 6.66)	0.930	0.328				

Data are presented as the regression coefficient beta (95 % confidence interval) from linear regression analyses adjusted for age, BMI and educational level.
Abbreviations: NW: normal weight, OW/OB: overweight/obesity, BMI: Body mass index, LC/HC: low calorie/high calorie; ANT: attentional network test, IGT: Iowa gambling test.
[§] Robust linear regression analysis.

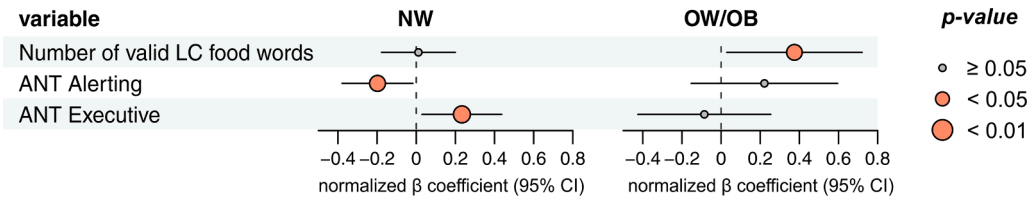

Fig. 2. Forest plot showing the z-score normalized regression coefficient beta (95 % confidence interval) from linear regression analyses for associations between fasting LEAP2 concentration as a predictor of behavioral tests outcomes in participants with NW and with OW/OB.

3. Results

3.1. Characteristics of the participants

The study included 199 males with a mean age (range) of 26 (18–40) years. Based on BMI, 108 participants were categorized as with NW, and 91 as participants with OW/OB. Of the recruited participants, none met criteria for underweight. Table 1 details participant characteristics. Plasma concentrations of LEAP2 were higher in participants with OW/OB. One hundred and ninety-nine participants completed the Stroop Food Task, and the number of valid neutral and food words was lower in individuals with OW/OB than NW participants. One hundred and thirty-two participants completed the Stroop LC/HC food task, the ANT, and the IGT. The number of valid neutral and food words in the Stroop LC/HC food task was lower in individuals with OW/OB than NW participants. Outcomes of the ANT and IGT did not differ between individuals with NW or OW/OB, except for the IGT total score, which was higher in individuals with OW/OB. Although the median IGT total score was identical in both groups (100), a significant group difference was detected ($p = 0.014$), likely reflecting differences in the score distribution, as the OW/OB group showed greater variability and a higher mean. When the IGT score was expressed as mean (SD), higher values were observed in the OW/OB group [101.17 (3.48)] vs the NW group [99.79 (4.44)].

3.2. LEAP2 concentration is associated with attention and the number of valid low-calorie food words depending on BMI category

Table 2 shows the associations of fasting LEAP2 concentration as a predictor of behavioral tests outcomes. Plasma LEAP2 concentration did not show associations with the outcomes of the Stroop Food and Stroop LC/HC food tasks, ANT, or IGT. Statistically significant interactions between BMI and plasma LEAP2 concentrations were observed for the number of valid low-calorie food words in the Stroop LC/HC food task, and the Alerting and Executive components of attention in the ANT (p for multiplicative interaction <0.05). When analysing participants with NW and OW/OB separately (Table 2, Fig. 2), LEAP2 concentration displayed a positive relationship with Executive attention (responsible for

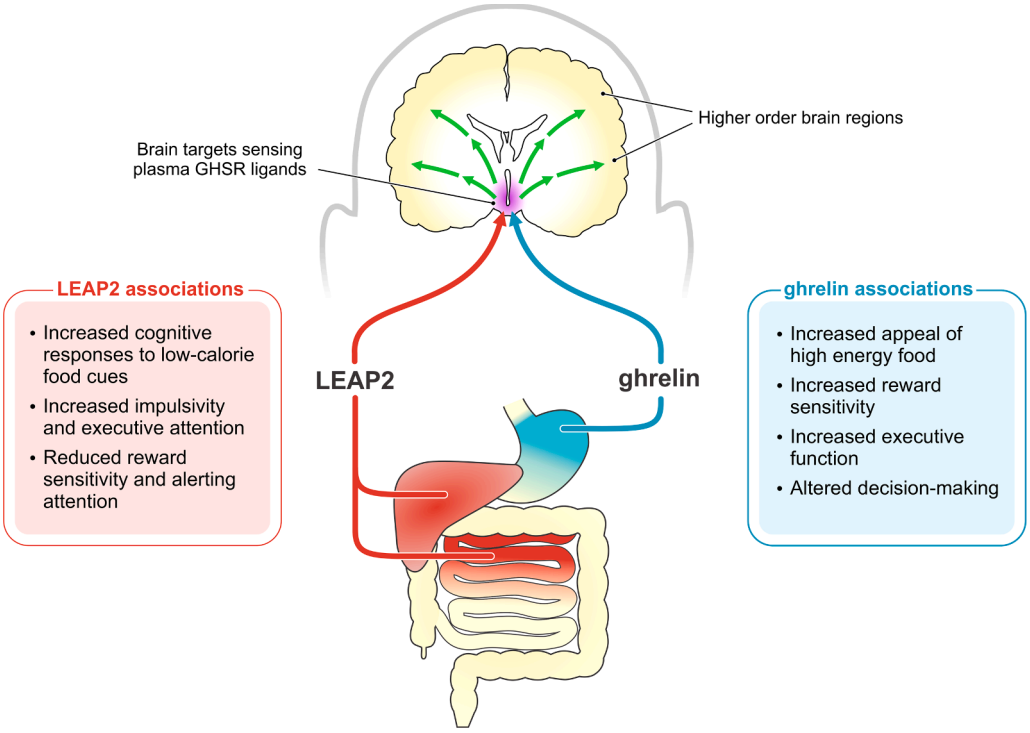

Fig. 3. Summary of how plasma concentrations of GHSR ligands, LEAP2 and ghrelin, are associated with specific behaviors in humans.
This figure is intended to place the current findings within a broader conceptual framework of GHSR ligands' function, integrating them with prior literature to illustrate potential mechanisms by which plasma concentrations of LEAP2 (red) and ghrelin (blue) may differentially modulate behavior in humans. LEAP2 was shown to be associated with enhanced cognitive responses to low-calorie food cues and executive attention, as well as with increased impulsivity and reduced reward sensitivity [9] and alerting attention. Conversely, ghrelin has been linked to increased appeal of high-energy food [48], heightened reward sensitivity [49], improved executive function [50], and altered decision-making [51]. In this hypothetical model, both peptides act on specialized brain regions that sense circulating signals (violet), which then relay information to intermediary areas and ultimately to higher-order cortical regions (green arrows) that influence reward processing, attention, and decision-making related to food.
Abbreviations: LEAP2: liver-enriched antimicrobial peptide 2.

resolving conflicts), and a negative association with Alerting attention (involved in sensitivity to incoming stimuli) only in participants with NW. In addition, a positive relationship with the number of valid low-calorie food words was observed only in participants with OW/OB. LEAP2 concentration exhibited a direct relationship with BMI [Beta (95 % CI): 1.53 (0.17; 2.90) $p = 0.028$] and waist circumference [Beta (95 % CI): 6.23 (1.05; 11.40) $p = 0.019$] only in participants with OW/OB, consistent with findings previously reported in the larger study sample [9].

4. Discussion

Our findings provide the first evidence that plasma LEAP2 concentration is associated with attention and cognitive responses to low-calorie food cues. Therefore, it is possible that LEAP2 not only acts as an anorexigenic signal but may also lead to prioritizing low-calorie food consumption.

Attentional processes and cognitive interference related to food have been implicated in obesity [17,30–32], as well as in eating disorders [33,34]. Attentional bias toward food images is associated with elevated body weight [22], and weight-loss maintainers exhibit reduced cognitive interference from food cues [17]. However, the role of appetite-regulating hormones in these behavioral changes remains unclear. In this study, we used two Stroop tasks to assess complementary aspects of food-related cognitive control. The variant of the Stroop Food Task used in this study measured response accuracy based on the number of valid words identified, providing a broad indication of general cognitive control and the ability of the individuals to inhibit distraction by food-related versus neutral stimuli. The Stroop LC/HC Food Task evaluates more specific cognitive control on different food types, allowing a finer analysis of distractors. This dual approach improves construct validity and interpretability, and supports detailed exploration of associations with plasma LEAP2 levels. Accuracy-based outcomes of Stroop tasks have been shown to provide meaningful insights into cognitive control in similar paradigms [15]. Our findings, using a Stroop Food paradigm, show that participants with OW/OB named fewer valid neutral and food-related words than participants with NW within the same time limit, suggesting a different cognitive response to both food and non-food cues that may indicate reduced inhibitory control [17]. This reduced performance may reflect diminished executive control in the presence of food-related cues, potentially contributing to maladaptive eating behaviors and difficulty in regulating food intake. Our observed altered response to the Stroop Food task aligns with previous studies showing that subjects with OW/OB exhibit delayed color-naming for food-related words [18,19], although one study found no differences in attentional processing between subjects with NW and OB [32]. To minimize the potential confounding effects of acute hunger—known to be more variable and pronounced in individuals with overweight or obesity [35]—the calorie-specific Stroop task was administered in the fed state. Although LEAP2 concentrations were measured in the fasted state, unpublished results from our group indicate that LEAP2 levels remain stable within 30 min after food intake. This supports the usefulness of fasting LEAP2 levels in relation to cognitive performance in the early postprandial period. However, Stroop task results obtained later (e.g., two hours after food intake) may differ and could show different associations with LEAP2 concentrations measured at that time. Additionally, while prior studies have shown that a 12-hour fast does not significantly affect performance in either the classic Stroop task [36,37] or in a Food Stroop task [38], these findings were derived exclusively from samples of normal-weight individuals and may not generalize to populations with OW or OB.

Current observation that fasting plasma LEAP2 concentration is associated with cognitive responses to LC, but not HC food cues in subjects with OW/OB suggests that this recently recognized hormone may influence food selection or preferences, particularly by prioritizing low-calorie options. These observations align with preclinical studies showing that GHSR strongly regulates food reward-related behaviors [39] and that centrally injected LEAP2 reduces binge-like eating of a palatable diet and memory for highly preferred foods [40,41]. The positive association between LEAP2 and the cognitive responses to low-calorie foods might indicate that LEAP2 influences how subjects with OW/OB perceive or respond to food cues, as higher LEAP2 levels may enhance cognitive focus on low-calorie foods as a compensatory mechanism for energy imbalance or metabolic dysregulation. The current findings are in line with the notion that LEAP2 functions as an endocrine signal involved in the regulation of appetite and may play a role in the cognitive processes underlying food choices and eating behavior in subjects with OW/OB. Notably, previously published results based on the same cohort from this study show that plasma LEAP2 concentration is directly associated with motor impulsivity, and inversely associated with reward responsiveness exclusively in subjects with OW/OB [9]. Therefore, LEAP2 may play a differential role in specific cognitive responses related to food intake in subjects with OW/OB. Altogether, our results reinforce the potential involvement of appetite-regulating hormones in human eating behavior and propose biological targets as the foundation for future therapeutic strategies.

Interestingly, the potential role of LEAP2 in attentional processes appears to be prominent only in lean subjects. In subjects with NW, higher LEAP2 levels were associated with enhanced executive attention; therefore, our study suggests that LEAP2 may influence cognitive functions related to planning and goal-directed behavior. Conversely, the inverse relationship between LEAP2 and alerting attention indicates that higher LEAP2 levels are linked to a reduction in alerting attention—the ability to maintain a heightened readiness to respond to incoming stimuli. This could suggest a trade-off where LEAP2 enhances executive functions at the cost of alerting attention, or it may reflect a more intricate interaction between metabolic and cognitive processes specific to lean subjects. The observed association between LEAP2 concentration and both alerting and executive attention in NW subjects, but not in those with OW/OB, suggests that the influence of LEAP2 on attentional networks may be diminished or lost in obesity. Here, we could not unmask any association between LEAP2 and decision-making, as assessed by the IGT. However, a previous study reported that LEAP2 can predict decision-making distortions in individuals with gambling disorders [24]. These findings suggest that the effects of LEAP2 on decision-making may be specific to gambling-related cognitive distortions. Understanding the neurobiological mechanisms behind these findings could be crucial for developing targeted dietary interventions or behavioral strategies for obesity treatment. Interventions aimed at modulating LEAP2 levels may have the potential to influence dietary habits and support weight management.

The neurobiological mechanisms underlying the associations between LEAP2 and food cue-related behavioral outcomes remain unclear. Functional imaging studies have helped to identify the brain regions involved in the performance of the ANT and Stroop tests. The neural networks of attention measured by the ANT appear to engage distinct brain regions: the alerting function is associated with various frontal and parietal regions, with strong thalamic involvement; the orienting network is linked to parietal sites and the frontal eye field; and the executive network is primarily connected to the anterior cingulate cortex and dorsolateral prefrontal cortex [20]. The Stroop Task performance, on the other hand, predominantly activates the right cingulate cortex, left dorsolateral prefrontal cortex, bilateral inferior frontal gyrus, right superior frontal gyrus, and temporal cortex [42]. Notably, a recent study found that postprandial plasma LEAP2 concentrations positively correlate with cue reactivity to foods in the anteroposterior cingulate cortex, paracingulate cortex, frontal pole, and middle frontal gyrus [11] suggesting a functional link between plasma LEAP2 and the brain areas involved in ANT and Stroop tests. In contrast, neuroanatomical studies in rodents and primates, including humans, indicate that GHSR is not significantly expressed in thalamic and cortical brain areas. Still, it is highly expressed in brain regions involved in the homeostatic regulation

of food intake, such as the hypothalamus, as well as in areas affecting reward-related aspects of feeding, including the hippocampus and mesolimbic system [43–46]. Additionally, studies in rodents showed that circulating factors, including ghrelin, do not significantly influence GHSR-expressing neurons located in brain regions distant from circumventricular organs [47]. Thus, it is highly likely that plasma LEAP2 and ghrelin target specific subsets of neuronal circuits specialized in sensing circulating factors, which relay information to intermediary brain regions that then connect to higher-order cortical areas, ultimately modulating attention and food-related decision-making. Our current findings show that LEAP2 is associated with cognitive responses to low-calorie food cues and executive attention, complementing earlier results from the same cohort that link this hormone to increased impulsivity and reduced reward sensitivity in men and women with OW/OB, but not with NW [9]. Additionally, previous analyses from this cohort suggest that the composition and caloric content of a meal can influence postprandial LEAP2 concentration [12], potentially regulating performance on feeding behavior tasks—particularly the Stroop LC/HC Food Task, which was performed after the meal. These effects contrast with those of ghrelin, which has been shown to enhance the appeal of high-energy food [48], increase reward sensitivity [49], improve executive function [50] and influence decision-making processes [51] (Fig. 3). Together, these findings underscore the opposing roles of ghrelin and LEAP2 within the GHSR system in modulating food-related cognition and behavior.

The strengths of the present study include the large sample size compared to previous studies [7,8,11] and the adjustment of analyses for potential confounding factors. However, several limitations influence the conclusions that can be drawn from this study. First, we only included male participants from the original study [9], as we did not have complete data on behavioral tests outcomes from females. Also, we could not measure plasma ghrelin concentration due to the lack of protease inhibitors in the sample collection. Our study did not specifically recruit participants with obesity; therefore, the OW/OB group was composed mainly of participants with BMI<33 kg/m^2. Since our study included men of mainly northern European origin, our findings might be not generalizable to other ethnic groups. Lastly, as the Stroop tasks was paper-based, trial-by-trial timing, word duration, or interstimulus intervals could not be recorded.

In conclusion, our study presents new evidence that LEAP2 is linked to attention and cognitive responses related to eating behaviors. Given that LEAP2 has been relatively recently described and that extensive and consistent data is still lacking, these insights highlight the potential of LEAP2 as a target for developing interventions to improve feeding behavior and address eating disorders and obesity.

CRediT authorship contribution statement

María F. Andreoli: Writing – original draft, Methodology, Formal analysis, Data curation. **Pablo N. De Francesco:** Visualization, Investigation, Formal analysis, Data curation. **Olga E. Titova:** Investigation, Formal analysis, Data curation. **Mario Perello:** Methodology, Investigation, Formal analysis. **Helgi B. Schiöth:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest. The sponsors had no role in the design of the study, the collection, analyses or interpretation of data, writing of the manuscript, or the decision to publish the results.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2025.115049.

Data availability

Data will be made available on request.

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