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## Full Title

**Differential Effects of Hunger on Cerebral Blood Flow in Healthy Adolescents**

## Short Title

**Effects of Hunger on Cerebral Blood Flow**

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## Abstract

Adolescence represents a key developmental period in terms of both mood and overweight and is linked to disturbed eating behavior. Therefore, it is essential to investigate the basis of food intake in healthy adolescents by considering mood impacts which remain largely unexplored.

Hence this study aims to investigate the impact of hunger and mood on cerebral blood flow (CBF) changes in healthy adolescents.

Fifteen participants underwent two MRI sessions including a 3D pseudo-continuous arterial spin labeling sequence: pre-lunch (hunger) and post-lunch (satiety). Mood was assessed using the Multiscore Depression Inventory for Children.

We found higher CBF values in the posterior insula in response to hunger compared to satiety, an area of the brain which contributes to the anticipation and motivation of feeding. In response to satiation, we observed higher CBF values in the precuneus, lingual gyrus and cuneus which are involved in the aspects of response inhibition related to food intake.

Furthermore, we show that correlation between mood assessment and CBF is modulated by appetite in the precuneus, anterior cingulate gyrus, anterior orbitofrontal gyrus, occipital gyrus and cuneus, suggesting that participants affected by depressed mood could use ruminative processing in order to evaluate the reward of an upcoming meal.

## Keywords [MeSH]

- Adolescent
- Cerebrovascular Circulation
- Mood
- Healthy Volunteers
- Hunger

## 1. Introduction

Food intake represents periodic behavior regulating body weight by obtaining the nutritional resources essential for survival. It involves complex homeostatic and non-homeostatic mechanisms which leads transient glycemc changes by stimulation and inhibition feeding and appetite<sup>1</sup>. Energy and weight regulation are thus directly link by the control of feeding in response to metabolic needs as well as by the experiences and hedonic aspects of food (psychological factors). Unfortunately, more than 300 million people worldwide are thought to suffer excessive food intake driving up obesity rates, especially in children and adolescents<sup>2,3</sup>. Such observations are not surprising due to the fact that puberty is usually characterized by psychological changes (depression, anxiety, stress etc.) influencing food choice and intake<sup>4,5</sup>. Indeed, it has been widely demonstrated that appetite is influenced by mood and emotional states such as depression, resulting in the consumption of palatable “comfort foods” (i.e. high-fat meals) as a means of alleviating negative feelings<sup>6</sup>. Given the complexity of the notion of food intake, knowledge regarding the neural substrates of appetite is rather limited; hence the necessity of investigating the basis of hunger and satiety states in healthy adolescents.

Most studies have investigated neural substrates using functional MRI in adult populations. They focus on visual presentations by varying appetizing value by means of neutral, low-calorie and high-calorie food picture stimulation. They demonstrate that the food pictures activate two gustatory processing brain areas devoted to the reward value of taste: the orbitofrontal and temporo-insulo-opercular cortices<sup>7-9</sup>. However, none of these trials recognize that specific types of food tend to be preferred under certain psychological conditions<sup>6</sup>. Therefore, some authors have investigated the effect of food deprivation on brain networks by comparing two states: “hunger” meaning a great desire for food and “satiety” meaning fullness<sup>10-13</sup>. Two studies using arterial spin labeling (ASL) imaging investigated mean CBF changes after consumption of either a high-fat meal or a water load<sup>13</sup> or high-fat yogurt<sup>12</sup>. Although CBF was found to increase at 40 min post-meal after the water load in the thalamus and insula, it decreased in the hypothalamus and insula at 65min-120min post-meal after the high-fat meal or high-fat yogurt. Furthermore, positron emission tomography (PET) imaging of regional CBF demonstrated an increase in the vicinity of the hypothalamus, thalamus, putamen, insular cortex, orbitofrontal cortex and limbic areas in response to hunger<sup>10,11</sup>. Higher regional CBF has also been reported in the prefrontal cortex and inferior parietal lobule in response to satiety.

However, all of these neuroimaging studies neglect the link between mood, emotional state, and feeding, as mentioned above. Some authors limit their investigation to exploring the “depression” effect found in individuals exhibiting symptoms of depression yet who fail to reach clinically significant levels that are common in the general population<sup>14-16</sup>. Their main aim was to investigate the effect of depression on structural changes in the hippocampus in healthy populations. They revealed bilateral hippocampal volume reduction which may predict subclinical depressive phenomenology in healthy adults. Unfortunately, none of the studies addressed the depressed mood effect in healthy populations in relation to the whole

brain and even less so in the context of food. Furthermore, all of these studies are based on healthy adults and none focus on the adolescent population.

Therefore, the aim of the present research is to broaden knowledge of the brain metabolism involved in the food intake of healthy adolescents using arterial spin labeling. We expected cerebral blood flow in areas of the brain governing taste: (i) to be implicated in response to hunger compared to satiety and (ii) to be correlated to mood.

## 2. Materials and Methods

### 2.1. Population

Fifteen healthy right-handed adolescents (7 female; 8 male; age=14.1±1.3 years, mean±SD) with no history of eating disorders or other medical illnesses participated in this study. All of the participants were right-handed and weight was normal (body mass index – BMI=19.3±1.7 kg/m<sup>2</sup> mean±SD). Mood assessment was measured in all of the adolescents using the Multiscore Depression Inventory for Children (MDI-C), comprising anxiety, self-esteem, sad mood, instrumental helplessness, social introversion, low energy, pessimism and defiance subscales. The total depression score was defined as the sum of these subscales and was converted to standardized scores – T scores<sup>17</sup>. Clinically significant depression was defined using a cut-off score of 56 or greater. This composite score is representative regardless of the sample size.

The study was conducted according to the Declaration of Helsinki and received ethical approval from the local ethics committee. Written informed consent was obtained from each participant (ClinicalTrials.gov Identifier: NCT02868619).

### 2.2. Study procedures

All participants underwent two MRI sessions: (i) one pre-lunch called hunger session and (ii) post-lunch called satiety session. They were prevented from eating at least 6h before the first MRI session, after which a standardized lunch was provided including bread, mini pasta shells (125g) with a portion of butter and gruyere, tomato sauce (300g), yogurt and compote. The second MRI session was performed one hour later when participants had reached a state of satiety<sup>18</sup>. Mood assessment was performed immediately after the meal.

### 2.3. MRI data acquisition

Neuroimaging data were collected using a 3T magnet (Skyra, Siemens, Germany) with a 32-channel head coil for each MRI session. Structural images (3DT1-MPRAGE) were acquired using the following parameters: echo time (TE) = 2.5ms; repetition time (TR) = 1690ms; flip angle = 9°; inversion time = 922ms; voxel size = 0.98x0.98x1 mm<sup>3</sup>; 176 slices. CBF data were acquired using a prototype sequence of 3D pseudo continuous arterial spin labeling (pCASL) according to parameters as follows: post-labeling delay (PLD) = 1800ms; bolus duration = 1800ms; TE/TR = 15.5/4600ms; 42 slices; voxel size = 1.64 x 1.64 x 3 mm with interpolation in acquisition plane.

### 2.4. MRI data pre-processing

Arterial spin labeling images were realigned to the baseline magnetization  $M_0$  image acquired with a long repetition time.

The label images were then subtracted pair-wise from the time-matched control images using surround subtraction to acquire perfusion-weighted images.

To ensure an accurate estimation of the cerebral blood flow (CBF), Asllani et al's partial volume effect (PVE) correction<sup>19</sup> was implemented in MATLAB and applied in native space, using a 7 x 7 x 1 voxel regression kernel. Briefly, it considers that the measured signal is a ponderation of gray matter, white matter and cerebrospinal fluid contribution:

$$\Delta M = P_{GM} * \Delta M_{GM} + P_{WM} * \Delta M_{WM} + P_{CSF} * \Delta M_{CSF}$$

Where  $P_{GM}$ ,  $P_{WM}$  and  $P_{CSF}$  are segmented posterior probabilities obtained from a high resolution T1 image,  $\Delta M$  the control-label differences from the ASL sequence in a voxel and  $\Delta M_{GM}$ ,  $\Delta M_{WM}$  and  $\Delta M_{CFS}$  the proper differences for each tissue in this voxel. Assuming a constant perfusion across a local 2D kernel (7x7), a system of equations can be defined to estimate  $\Delta M_{GM}$ ,  $\Delta M_{WM}$  and  $\Delta M_{CFS}$  through a least square approach.

CBF computation was performed using a one compartment model<sup>20</sup>:

$$CBF = \frac{6000 \cdot \lambda \cdot \Delta M \cdot e^{\frac{PLD}{T_{1,blood}}}}{2 \cdot \alpha \cdot M_{0b} \cdot T_{1,blood} \cdot \left(1 - e^{-\frac{\tau}{T_{1,blood}}}\right)} \quad [ml/100g/min]$$

where  $\Delta M$  represents mean difference in signal intensity between label and control images,  $\lambda$  equals blood/tissue water partition coefficient,  $T_{1,blood}$  equals longitudinal relaxation time of blood,  $\alpha$  is inversion efficiency,  $\tau$  label duration, and  $M_{0b}$  blood magnetization.

We chose to use the estimation of gray matter  $\Delta M$  and  $M_{0b}$  provided by PVE correction to compute gray matter CBF. Blood magnetization ( $M_{0b}$ ) was estimated using local tissue perfusion<sup>21</sup>.

The parameters used for quantification were: labeling efficiency = 0.85; longitudinal relaxation,  $T_{1,blood} = 1650$  ms; and, as we focused on gray matter,  $\lambda_{GM} = 0.98$ .

Overall mean gray matter CBF was retrieved from the PVE-corrected CBF map in subject space, then normalized to the MNI (Montreal Neurological Institute) space.

## 2.5. MRI statistical analyses

The normalized CBF maps were entered into whole brain voxel-wise general linear model analysis using the SPM12 toolbox. Paired t-tests were conducted to examine CBF changes during both states (hunger and satiety). To limit the analysis to gray matter, a mean gray matter mask was generated by thresholding each subject's spatially normalized GM probability map to 0.8. Only voxels considered as cortical gray matter in all subjects were included in the mask. Furthermore, voxel-based morphometry (VBM) analysis was undertaken to assess the relationship between (i) CBF and total depression scores and (ii) CBF and BMI with respect to each state as well as to the comparison of two states. For this, the normalized CBF maps have been subtracted between hunger and satiety state, then resulting delta images have been entered in the VBM analysis. These VBM analyses aimed to identify differences in the local composition of brain tissue<sup>22</sup>.



All results were age- and sex-adjusted using two covariates of no interest in the general linear model (GLM) that is fit to each voxel's data. Results were reported with a statistical p-value threshold corresponding to  $p < 5 \cdot 10^{-4}$  voxel-based with a minimum cluster size of 30 voxels, uncorrected; and  $p < 0.05$  cluster-based, FDR corrected.

In addition, the estimated parameter values ('beta' images) were extracted from VBM analyses in each peak score T for each subject. Then, a correlation analyses were performed between beta values and total depression scores. They were carried out using the R software, version 3.1.0.

Being that the size of our sample is low ( $n=15$ ), non-parametric tests were also performed for the paired-t-test using TFCE (Threshold-Free Cluster Enhancement) method, as described by Han et al. 2019. It consists to a generalized combination of cluster size and voxel intensity to increase statistical power<sup>23,24</sup>. Our results were very similar than those by using the classic method, therefore they were not reported here for clarity (available on request).

### 3. Results

#### 3.1. Participant characteristics

Among the participants only one individual was clinically diagnosed with depression ( $T > 56$ ) and was excluded from analysis. The mean total depression score (mean $\pm$ SD) was 45.9 $\pm$ 8.2.

Furthermore, no correlation was found between CBF and BMI during hunger and satiety state separately as well as in the difference (hunger vs satiety).

#### 3.2. CBF in hunger vs satiety states

Brain regions showing significant differences between hungry and satiated states are illustrated in Figure 1 and Table 1 with a statistical threshold of  $p < 5 \cdot 10^{-4}$  voxel-based, uncorrected and  $p < 0.05$  cluster-based, FDR corrected.

By comparison with a state of satiety, during a state of hunger CBF increased significantly in the bilateral posterior insula.

By comparison with a state of hunger, a state of satiety showed significantly higher CBF within the right cuneus, left lingual gyrus and left precuneus.

#### 3.3. CBF and mood

Results of whole-brain voxel-based morphometry in relation to CBF and total depression scores in each state are reported in Figure 2 and Table 2 with a statistical threshold of  $p < 5 \cdot 10^{-4}$  voxel-based, uncorrected and  $p < 0.05$  cluster-based, FDR corrected.

During hunger, CBF increased proportionate to higher total depression scores in the right superior and inferior occipital gyrus, bilateral cuneus, left precuneus, left anterior cingulate gyrus, right anterior orbitofrontal gyrus and left cerebellum. No correlation was found for satiety and the comparison hunger vs satiety.

During hunger, a significant correlation was observed between the CBF and total depression score in the right superior occipital gyrus ( $R^2=0.78$ ,  $p=3.11e-05$ ), right inferior occipital gyrus ( $R^2=0.77$ ,  $p=3.49e-05$ ), left precuneus ( $R^2=0.75$ ,  $p=6.16e-05$ ), left anterior cingulate gyrus ( $R^2=0.74$ ,  $p=7.16e-05$ ), right anterior orbitofrontal cortex ( $R^2=0.73$ ,  $p=9.02e-05$ ), left cerebellum ( $R^2=0.71$ ,  $p=1.42e-04$ ), right cuneus ( $R^2=0.64$ ,  $p=5.97e-04$ ) and left cuneus ( $R^2=0.69$ ,  $p=2.53e-04$ ). The scatterplots were reported in the figure 3 in order to better represent the dispersion of data.

## 4. Discussion

The present study aims to explore the impact of hunger and mood on cerebral blood flow changes in healthy adolescents using arterial spin labeling.

Our results reveal that hunger is associated with increased CBF in the bilateral posterior insula, which is an area previously described as important in the anticipation and motivation of feeding. In contrast, satiation is associated with increased CBF in the left precuneus, left lingual gyrus and right cuneus which are involved in the aspects of response inhibition related to food intake.

This comparison between states of hunger and satiety has enhanced our findings by using a most reproducible and robust ASL imaging sequence<sup>25</sup>. In the literature, certain authors focused on a pulsed ASL sequence<sup>12,13</sup> while we used a 3D pseudo-continuous ASL sequence that is a typical approach in the context of clinical imaging, providing superior labeling efficiency and better compatibility of body coil RF transmission<sup>25</sup>.

Furthermore, we have shown that correlation between CBF and total depression scores was modulated by appetite in the left precuneus, left anterior cingulate gyrus, right anterior orbitofrontal gyrus, left cerebellum, bilateral cuneus and right inferior and superior occipital gyrus. However, these results have been reported only in the hunger state but not in the comparison between hunger vs satiety. Therefore, all of these confirm evidence of a moderate relationship between mood and appetite even in participants unaffected by depression, suggesting that adolescents could have subclinical symptoms of depression hence concurring with findings in the literature in healthy adult populations<sup>14-16</sup>. Indeed in our study, adolescents had total depression scores below the clinical threshold of depression but the subscale scores had a tendency to vary which may account for mood fluctuations in our participants and CBF variations.

### 4.1. CBF in hunger vs satiety states

We found that CBF was significantly increased in the bilateral posterior insula when hungry compared to when satiated. This finding is in line with previous fMRI research reporting that the insula is activated when hungry relative to when satiated, and during visual presentation of high-calorie food pictures relative to neutral pictures<sup>26,27</sup>. Furthermore, ASL and PET imaging of regional CBF studies confirms these results by showing that CBF in the insula increases before liquid meal ingestion<sup>10</sup> and decreases after administration of a liquid meal, high-fat yogurt or a high-fat meal<sup>11-13</sup>. Based on other studies highlighting a link between regional CBF changes in the insula and the motivational value of chocolate<sup>9,28</sup>, certain authors have suggested that CBF changes in the insula are modulated by motivational factors such as feeling hungry. Another hypothesis is that such changes could also be linked to alteration in insulin concentration. Tataranni et al. have reported in extreme fast of 36h that an increase in plasma insulin concentration is correlated with a regional CBF decrease in the insula, supporting the hypothesis of the anorectic role of insulin<sup>10</sup>. Therefore, the transition from hunger to satiety could result in changes in insulin levels in response to meals through a

decrease in CBF in the insula which may be modulated by feelings of hunger, playing an essential role in food-related motivation. This result concurs with our findings which show an increase in CBF before food-intake corresponding to a decrease in CBF when satiated as described in the literature. In this way, other authors established that the posterior insula could dynamically contribute to conscious interoceptive using a posterior-to-anterior gradient within insular cortex<sup>29-32</sup>. Prediction-error information of interoception would be processed in the posterior insula, whereas the cognitive and motivational information of interoception would be integrated in the anterior insula. Consequently, interoceptive awareness of variations from energy homeostasis can be a crucial part in the activity of insular cortex. Hunger feeling could lead to greater interoceptive prediction signals by anticipating of the food intake which could explain the increase of CBF observed during hunger compared to satiety.

By comparison with hunger, we have identified a significant increase in CBF in the left precuneus during satiety. This region, known to exhibit decreased activation during goal-directed action, has been shown to participate in abstract visuospatial mental imagery and self-processing operations<sup>33,34</sup>. Recent fMRI research has reported that meal ingestion increases activity in the precuneus suggesting that involvement of the precuneus would appear to be essential in the processing of satiety<sup>35</sup>. The authors speculate that ingestion of a recent meal leads to changes in the imagined or anticipated taste of the food which may influence prospective food consumption by consciously suppressing of food cravings. In contrast, two PET studies were agreed to provide evidence that the hunger (before liquid meal ingestion) was associated with increased CBF in the bilateral precuneus<sup>10</sup> or that the satiation was associated with decreased CBF bilaterally in the precuneus<sup>36</sup>. This change is interpreted as an increase in the attention and salience-encoding for the food when the appetite is high<sup>37,38</sup>. The discrepancies between all these studies could be explained by the differences between PET and fMRI imaging methodologies. We can also note that these studies have been performed with a shift of around 15 years which could explain the mismatches due to large advances in MRI technology and imaging analysis. Despite the lack of consensus, our results are in concordance with recent fMRI finding of Cheah<sup>35</sup> and indicate that this functional increase in activity could be associated with the change in cerebral blood flow that was observed in our results. This could suggest the involvement of precuneus in the processing of satiety by consciously reducing food cravings.

Furthermore, during satiety by comparison with hunger, we observed increased CBF in the left lingual gyrus and right cuneus, areas known to be involved in visual processing<sup>39</sup>. Although rarely discussed, both of these regions have often been associated with the visual presentation of food especially in high-calorie activation<sup>26,40-42</sup>. This confirms the role of the left lingual gyrus and right cuneus in response to food cues. However, one fMRI study comparing satiety and hunger reported that the bilateral cuneus was only recruited during satiety<sup>43</sup>, in discordance with our results which suggest a right-lateralization of the response to the satiety. Authors was also demonstrated that the bilateral lingual gyrus was involved during hunger compared to satiety, inconsistent with our findings. Two hypotheses could be raised to explain these discrepancies. First, the authors included only female participants whereas we recruited 7 female and 8 male adolescents. Given that CBF varies from women to men<sup>44</sup>

especially concerning responses to satiation<sup>45</sup>, these sex differences could account for the discrepancies between our results and those found in the literature, although this effect has been corrected in our analysis. A second explanation could implicate the methodology due to the fact that the authors used fMRI with visual presentations of food whereas we focused on ASL imaging at rest without visual stimuli. Moreover, other fMRI studies have demonstrated that the left lingual gyrus was positively coupled with appetite inhibition and satiety in anorexics<sup>43,46</sup>. Therefore, in our study, it may be suggested that the left lingual gyrus and right cuneus – like the left precuneus described above – were instrumental in consciously suppressing eating.

On the basis of such concordance, our results support the idea that the functional changes reported in fMRI studies conceivably reflect the blood flow changes identified in this work.

#### 4.2. CBF and mood

We observed an influence of mood on CBF in terms of appetite only during hunger. Increased CBF was correlated with higher total depression scores in the precuneus, anterior cingulate gyrus, orbitofrontal cortex, cerebellum, cuneus and occipital gyrus.

Certain authors have reported that the left precuneus is metabolically overactive in treatment-resistant major depression<sup>47,48</sup>. Since the precuneus is involved in introspective processing, some authors have suggested that their findings may reflect a tendency towards rumination in depression, given that depressed individuals repetitively entertain these negative thoughts<sup>49</sup>. Furthermore, other studies related to resting-state functional MRI describe greater connectivity in the precuneus among patients with major depressive disorder<sup>50,51</sup>. This region constitutes a component of the default mode network (DMN) and underlies its participation in self-evaluation and emotional regulation<sup>52</sup>. Therefore, certain authors have interpreted their findings as changes in the DMN resulting in greater manipulation of negative emotional content, and they support the idea of a close relationship between increased CBF and excessive functional connectivity in depressed subjects<sup>50</sup>. In our study, we also observed that increased CBF was correlated with higher total depression scores in the precuneus occurring only when hungry. This suggests that the more participants tend to feel depressed, the more they focus on eating and ruminative processes when they are deprived of food.

These results are corroborated by Greicius et al.<sup>50</sup> who demonstrate that subjects affected by major depressive disorder show increased functional connectivity in the anterior cingulate gyrus. They support the hypothesis of hyper-connectivity in the DMN which may reflect constrained thinking as a ruminative process<sup>50,51</sup>. However, studies in ASL imaging (pulsed ASL) show inhomogeneous findings, reporting an increase<sup>53</sup> or decrease<sup>54,55</sup> in CBF in the anterior cingulate gyrus in cases of major depressive disorder. Our findings show a correlation between increased CBF and higher total depression scores in the left anterior cingulate gyrus among healthy adolescents in a state of hunger, in accordance with Duhamel et al.<sup>53</sup> The anterior cingulate gyrus is known to be involved in mood regulation and the processing of social information such as rewards, motivation, error monitoring and decision making<sup>56</sup>. This is consistent with our preceding assumption that, in a state of hunger, adolescents with higher

total depression scores tend to dwell on the same thought by focusing on the benefit of an upcoming meal as a reward.

Thus, we widen the scope of these results by showing a correlation between increased CBF and higher total depression scores in the right anterior orbitofrontal gyrus during a state of hunger. A number of studies have identified that the anterior orbitofrontal gyrus is positively related to the severity and various symptoms of major depressive disorder<sup>57-59</sup>, suggesting that this type of dysfunction could mediate the manifestation of depression. It has been reported that the right anterior orbitofrontal gyrus plays a critical role in abstract goal-oriented rewards<sup>60</sup> and in recognition memory<sup>61</sup>. Consequently, these findings confirm our hypothesis that participants affected by depressed mood and in fasting state are able to recall their past experience of food-motivated behavior in order to evaluate the reward of an upcoming meal.

Furthermore, we have observed that increased CBF is found to correlate with higher total depression scores in the bilateral cuneus and right occipital gyrus during a state of hunger. This concurs with the study conducted by Hwang et al. showing increased CBF in the right superior occipital gyrus and cuneus in depression<sup>62</sup>. These regions are known to participate in the processing of visual information and the generation of mental imagery<sup>39,63-65</sup>. We therefore postulate that a state of hunger could lead to anticipation of food intake using mental representations of meals among participants with higher total depression scores. They may retrieve previous food-related experiences from long-term memory into working memory to construct visual representations of food.

#### 4.3. Limitations

Nevertheless, most studies on regional CBF imaging by fMRI and PET have reported the involvement of the orbitofrontal cortex in food-related processes<sup>9-11,26,27</sup>. Consequently, we would expect to find CBF changes in this region with regard to appetite, yet no changes were observed when comparing states of hunger and satiety. Likewise, ASL studies reported no CBF changes in this region following consumption of a high-fat meal or water load<sup>13</sup> or high-fat yogurt<sup>12</sup>. A major explanation for this lack of activity could reside in imaging difficulties, causing magnetic susceptibility artifacts in the ventral brain areas especially when using high-field magnets; however we used pseudo-continuous ASL imaging which is known to demonstrate higher quality compared to the pulsed ASL sequences generally described in the literature. A second possible limitation addresses mood assessment that may be influenced by the reliability of the means of assessment since the measure of mood was self-reported. Furthermore, it might be worthwhile to perform this measure before the first MRI and after the second MRI scan to assess whether appetite influences participant responses. For our part we evaluated mood immediately after the meal, possibly entailing diminished impact of the appetite effect due to the fact that satiety had not yet been reached metabolically (postprandial phase). From a psychological perspective, the state of the participants would appear to represent neither hunger pangs nor complete satiety but may reflect a basal state, thus supporting the notion that total depression scores may be applicable to both states (hunger and satiety).

## **5. Conclusion**

To conclude, our study confirms, by means of more efficient ASL sequences, involvement of the posterior insula and precuneus in the modulation of hunger. We also highlight a hitherto unpublished observation indicating that feelings of hunger may moderately modulate the relationship between mood and brain activity in specific regions. These results suggest that participants with higher total depression scores may use ruminative processes and visual representations of food to evaluate the reward of an upcoming meal. Therefore, this study involving healthy adolescents opens the way to potential avenues of future research on eating disorders such as obesity. Further research could also incorporate connectivity analysis, to link the identified regions with CBF changes, into the functional networks involved in hunger and mood fluctuations, namely depression.

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## **7. Author Contribution statement**

Céline Charroud has a substantial contribution to the analysis of data, interpretation of data and the writing of the article.

Nicolas Menjot de Champfleur is involved in the revision of the article.

Emily Sanrey participates in concept and design, planned the acquisition and provided a feedback of the article.

Josef Pfeuffer conceived the design of ASL prototype sequence.

Jérémy Deverdun participates in the analysis of data.

Emmanuelle Le Bars contributes to the concept and design of the study and performs the critical revision of the article for important intellectual content.

Philippe Coubes directed the project and provided a feedback of the article.

All authors discussed the results and commented on the manuscript.

## **8. Declaration of conflicting interests**

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

All co-authors have seen and agree with the content of the manuscript. The authors hereby certify that the submission is not under review with any other publication. The authors declare that they have no conflict of interest.

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## 10. Appendix

### 10.1. Figure

#### 10.1.1. Figure 1

##### *Title*

Statistical parametric maps showing regions of cerebral blood flow changes in states of hunger and satiety.

##### *Footnotes*

During hunger compared to satiety, CBF increases in the bilateral posterior insula (red). During satiety compared to hunger, CBF increases in the right cuneus, left lingual gyrus and left precuneus (blue).

A statistical p-value threshold was used corresponding to  $p < 5 \cdot 10^{-4}$  voxel-based with a minimum cluster size of 30 voxels, uncorrected and  $p < 0.05$  cluster-based, FDR corrected. Results were age- and sex-adjusted.

Abbreviations: CBF, Cerebral Blood Flow; L, Left; R, Right.

##### *File name*

Figure1.png

#### 10.1.2. Figure 2

##### *Title*

Statistical parametric maps showing a positive correlation between blood flow and mood assessment when hungry.

##### *Footnotes*

Mood assessment was measured using total depression scores. When hungry, a correlation between increased CBF and higher total depression scores was identified in the precuneus, anterior cingulate gyrus, anterior orbitofrontal cortex, cerebellum, cuneus and occipital gyrus. No correlation was found when satiated.

A statistical p-value threshold was used corresponding to  $p < 5 \cdot 10^{-4}$  voxel-based with a minimum cluster size of 30 voxels, uncorrected and  $p < 0.05$  cluster-based, FDR corrected. Results were age- and sex-adjusted.

Abbreviations: CBF, Cerebral Blood Flow; L, Left; R, Right.

##### *File name*

Figure2.png

### 10.1.3. Figure 3

#### *Title*

Scatterplots of the correlation between blood flow and mood assessment when hungry.

#### *Footnotes*

Figure depicts mean CBF (beta value) in function of total depression score for each subject in regions

each peak score T.

Correlation analysis was performed in the right superior occipital gyrus ( $R^2=0.78$ ,  $p=3.11e-05$ ), right inferior occipital gyrus ( $R^2=0.77$ ,  $p=3.49e-05$ ), left precuneus ( $R^2=0.75$ ,  $p=6.16e-05$ ), Left anterior cingulate gyrus ( $R^2=0.74$ ,  $p=7.16e-05$ ), right anterior orbitofrontal cortex ( $R^2=0.73$ ,  $p=9.02e-05$ ), left cerebellum ( $R^2=0.71$ ,  $p=1.42e-04$ ), right cuneus ( $R^2=0.64$ ,  $p=5.97e-04$ ) and left cuneus ( $R^2=0.69$ ,  $p=2.53e-04$ ).

Abbreviations: a.u., arbitrary unity; CBF, Cerebral Blood Flow.

#### *File name*

Figure3.png

## 10.2. Table

### 10.2.1. Table 1

#### *Title*

Brain regions showing increased cerebral blood flow in states of hunger and satiety.

#### *Footnotes*

Results were evaluated using paired t-test analysis adjusting for age and sex. A statistical p-value threshold was used corresponding to  $p < 5 \cdot 10^{-4}$  voxel-based with a minimum cluster size of 30 voxels, uncorrected and  $p < 0.05$  cluster-based, FDR corrected. Results were age- and sex-adjusted.

Abbreviations: sc, same cluster; L, Left; R, Right.

#### *File name*

Table1.docx

### 10.2.2. Table 2

#### *Title*

Brain regions showing correlation between cerebral blood flow and total depression scores when hungry.



### *Footnotes*

Positive correlation was reported between cerebral blood flow and total depression scores during hunger. Results were evaluated using voxel-based morphometry analysis by adjusting for age and sex. A statistical p-value threshold was used corresponding to  $p < 5 \cdot 10^{-4}$  voxel-based with a minimum cluster size of 30 voxels, uncorrected and  $p < 0.05$  cluster-based, FDR corrected.

Abbreviations: sc, same cluster; L, Left; R, Right

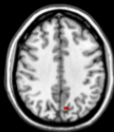
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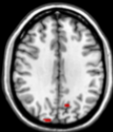


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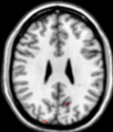
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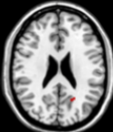
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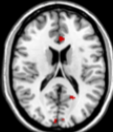
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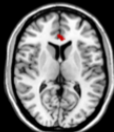


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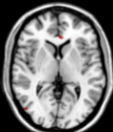


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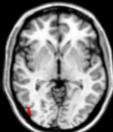
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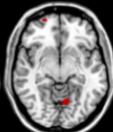
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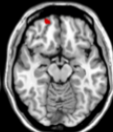
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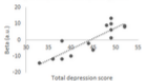
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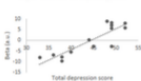
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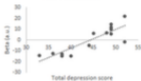
Right Superior Occipital gyrus



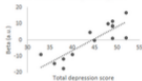
Right Inferior Occipital gyrus



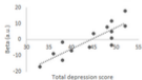
Left Precuneus



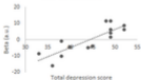
Left Anterior Cingulate gyrus



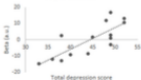
Right Anterior Orbitofrontal gyrus



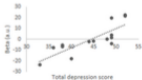
Left Cerebellum



Right Cuneus



Left Cuneus



Side	Structure	MNI coordinates [x,y,z]			Cluster size	Peak score T	P value (FDR corr)
Hunger>Satiety							
L	Posterior insula	-42	-18	-4	33	6.42	0.017
R	Posterior insula	40	-12	-4	114	6.01	<10 <sup>-3</sup>
Satiety>Hunger							
L	precuneus	-6	-56	58	64	5.65	0.001
L	precuneus	-2	-48	48	sc	4.45	0.001
L	Lingual gyrus	-8	-80	-6	95	5.29	<10 <sup>-3</sup>
L	Lingual gyrus	-8	-94	-6	sc	5.10	<10 <sup>-3</sup>
L	Lingual gyrus	-4	-68	4	sc	4.85	<10 <sup>-3</sup>
R	Cuneus	6	-76	26	77	5.15	<10 <sup>-3</sup>
R	Cuneus	2	-72	20	sc	5.03	<10 <sup>-3</sup>

Side	Structure	MNI coordinates [x,y,z]			Cluster size	Peak score T	P value (FDR corr)
R	Superior occipital gyrus	18	-92	32	39	6.46	0.006
R	Inferior occipital gyrus	48	-76	-2	47	6.38	0.002
L	Precuneus	-20	-58	20	34	6.01	0.006
L	Anterior cingulate gyrus	-6	30	14	101	5.91	<10 <sup>-3</sup>
R	Anterior orbitofrontal gyrus	20	58	-14	57	5.76	0.002
L	Precuneus	-12	-70	34	40	5.49	0.003
L	Cerebellum	-10	-64	-10	74	5.47	<10 <sup>-3</sup>
R	Cuneus	6	-94	16	33	5.12	0.006
L	Cuneus	-4	-90	18	sc	4.61	0.006