Assessing cognitive control and the reward system in overweight young adults using sensitivity to incentives and white matter integrity

Sussanne Reyes¹, Carolina de Medeiros Rimkus², Betsy Lozoff³, Bharat B. Biswal⁴, Patricio Peirano¹, Cecilia Algarín¹*

¹ Laboratory of Sleep and Functional Neurobiology, Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile, ² Department of Radiology and Oncology, Laboratory of Medical Investigation (LIM-44), Faculty of Medicine, University of Sao Paulo, Sao Paulo, Sao Paulo, Brasil, ³ Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan, United States of America, ⁴ Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, United States of America

* calgarin@inta.uchile.cl

Abstract

Cognitive control and incentive sensitivity are related to overeating and obesity. Optimal white matter integrity is relevant for an efficient interaction among reward-related brain regions. However, its relationship with sensitivity to incentives remains controversial. The aim of this study was to assess the incentive sensitivity and its relationship to white matter integrity in normal-weight and overweight groups. Seventy-six young adults participated in this study: 31 were normal-weight (body mass index [BMI] 18.5 to < 25.0 kg/m², 14 females) and 45 were overweight (BMI ≥ 25.0 kg/m², 22 females). Incentive sensitivity was assessed using an antisaccade task that evaluates the effect of incentives (neutral, reward, and loss avoidance) on cognitive control performance. Diffusion tensor imaging studies were performed to assess white matter integrity. The relationship between white matter microstructure and incentive sensitivity was investigated through tract-based spatial statistics. Behavioral antisaccade results showed that normal-weight participants presented higher accuracy (78.0 vs. 66.7%, p = 0.01) for loss avoidance incentive compared to overweight participants. Diffusion tensor imaging analysis revealed a positive relationship between fractional anisotropy and loss avoidance accuracy in the normal-weight group (p < 0.05). No relationship reached significance in the overweight group. These results support the hypothesis that white matter integrity is relevant for performance in an incentivized antisaccade task.

Introduction

Obesity is a condition associated with multiple comorbidities, including certain cancer types, diabetes, hypertension, osteoarthritis, metabolic syndrome, atherosclerosis, heart failure, and
and Food Technology, University of Chile. All data are available for researchers who meet the criteria for access to confidential data and does not involve the identification of our participants. Requests for these data may be sent to the group leader Dr. Cecilia Algarín (calgarin@inta.uchile.cl). Dr. Algarín will be responsible for the oversight of the banking of these data and review all requests to utilize the data and images. Researchers can also send data requests to the ethics committee in the Institute of Nutrition and Food Technology, University of Chile to the email address comite.etica@inta.uchile.cl.

**Funding:** This study was supported grants from the Chilean National Fund for Scientific and Technological Development (FONDECYT; No. 11160671) and National Institutes of Health (NIH HD33487). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

Cerebral structural networks mediate the behaviors related with obesity risk [7, 8], and thus studies that focus on specific brain mechanisms are required. Individuals express the desire to limit food consumption but nevertheless persist despite knowing the negative consequences. This fact suggests that obesity and addiction may share some cognitive features [9]. This addictive trait has been linked to dopamine (DA) signaling neuroadaptations in certain brain regions [10]. In obesity, decreases in DA brain signaling (receptors and release) have been also reported [11]. Studies suggest that obesity is at least partly the result of an imbalance in the DA reward system [12, 13].

Reward and loss incentives strongly motivate human behavior, and their interaction with cognitive control is crucial for goal-directed conduct [14, 15]. In this study, sensitivity to incentives was evaluated as the effect of reward and loss incentives on cognitive control [16, 17]. Previous evidence demonstrated differences in sensitivity to incentives related to obesity at different ages [16, 18–21]. Specifically studies in obese adults have shown reduced or similar sensitivity to incentives compared to lean subjects [18, 22, 23]. These variances affect decision making and play a key role in overeating behavior [20, 21]. Brain regions included in the circuitry that underlie incentive processing are the ventral striatum and prefrontal cortex [14, 24, 25], and the DA neurotransmission system plays a central role to ensure these networks function properly [14, 26].

Diffusion tensor imaging (DTI) is a non-invasive method to assess white matter (WM) integrity. The most commonly used DTI parameter is fractional anisotropy (FA); greater FA indicates higher WM integrity [27]. In adults, there is an inverse association between body mass index (BMI) and FA in the corpus callosum, fornix, thalamic radiation, internal and external capsules, uncinated fasciculus, longitudinal fasciculus and fronto-occipital fasciculus [7, 28–31]. Overweight (OW) adults also show lower FA in both frontal corticospinal tracts and brainstem compared with normal-weight (NW) peers [32]. These WM tracts relate to reward, emotions, and cognitive control [7, 27, 33, 34]. However, findings in this population have been controversial [7, 31, 35–39].

Through connecting brain areas, several WM tracts play crucial roles in the processing of rewarding stimuli [40, 41]. Neural responsiveness to incentives would be mediated by WM integrity through strengthening communication efficiency among brain regions [41, 42]. We previously explored the relationship between sensitivity to incentives and OW in adolescence [16]. In this study, we extended our results to young adulthood and focused on its association with WM microstructure. To the best of our knowledge, it remains unclear whether NW and OW individuals differ regarding the relationship between sensitivity to incentives and WM integrity.

The main aim of the current study was to assess the incentive sensitivity and its relationship with WM integrity in a sample of NW and OW young adults. Therefore, we tested whether (a) OW participants present lower incentive sensitivity (reward and loss) compared to NW participants and (b) the difference in sensitivity to incentives between groups is associated with WM integrity in tracts related to cognitive control and incentive sensitivity, as assessed by DTI.

**Materials and methods**

**Participants**

This cross-sectional study included 86 Chilean young-adults. These subjects represented a subset of those participating in a cohort follow-up study on early iron deficiency and
neurodevelopment jointly conducted by the University of Chile and the University of Michigan. They were enrolled in infancy between 1991 and 1996 in the southeast area of the city of Santiago, Chile. DTI studies were analyzed and neurophysiological evaluations were performed in the Sleep and Functional Neurobiology Laboratory, Institute of Nutrition and Food Technology (INTA), University of Chile.

The study design and findings during follow-ups have been published elsewhere [43–46]. In short, participants were healthy full-term infants (birth weight \(\geq 3.0\) kg, without perinatal complications and free of acute or chronic illnesses). Infants with iron-deficiency anemia identified at 6, 12, or 18 months were considered for neurofunctional assessments. Infants who clearly were non-anemic (venous hemoglobin [Hb] \(\geq 115\) g/L) were randomly invited to the control group. No participant had iron-deficiency anemia at subsequent ages. Follow-ups were performed at different ages between infancy and young adulthood.

All participants provided signed informed consent, according to the norms for Human Experimentation, Code of Ethics of the World Medical Association (Declaration of Helsinki, 1995). The original and follow-up protocols were approved and reviewed annually by the Institutional Review Boards of the University of Michigan, Ann Arbor, and the Institute of Nutrition and Food Technology, University of Chile, Santiago.

Ten participants were excluded from analysis: 3 for radiological abnormalities (subarachnoid cyst, vascular malformation, and cavum septum pellucidum), 3 for technical problems with incentivized antisaccade task recordings, 2 for movement artifacts in the DTI study, and 2 for technical differences in the DTI sequence. The excluded participants and final sample (\(n = 76\)) were similar with regards to background characteristics.

### Incentivized antisaccade task

The incentivized antisaccade task has been used to investigate the interaction between cognitive control, incentive (reward and loss) effects and their implications in decision-making processing [24–26, 47]. The neural circuitry that underlies behavioral performance has been well characterized in animals and humans [14, 24–26, 48].

**Design.** The incentivized antisaccade task is an oculomotor test that explores the ability to exert cognitive inhibitory control of behavior by employing voluntary suppression of a prepotent saccadic response (fast eye movements) in the presence of “reward”, “loss avoidance”, or “neutral” incentives [16, 47]. Participants had to inhibit an eye movement toward a visual stimulus and instead make a planned saccade to its mirror location (antisaccade). Each trial began with 2- or 3-s presentation of one of the three possible incentive types:

a. **Reward:** An image of a 1,000 Chilean peso bill (US$ 1.5) indicated a monetary gain if they performed the trial correctly, i.e., an antisaccade. An error did not result in “loss of money”.

b. **Loss avoidance:** A torn bill image of the same amount indicated a monetary loss if an incorrect saccade was made. The correct response did not result in a “gain of money”.

c. **Neutral:** A green rectangle indicated no incentive, i.e., no money was “gained” or “lost”, and regardless of performance, the amount of money remained the same.

Following one of these incentive images, a peripheral target (a small yellow dot) appeared for 1.0 s at one location (to the left or right of the screen center) to indicate that an antisaccade must be completed (response phase). Finally, a central stimulus appeared for 1.0 s to center the subject’s gaze before the next trial (Fig 1). They were encouraged to perform the task as well and quickly as possible regardless of incentive type. During the task, they did not receive...
feedback about their performance. Twenty reward, 20 loss avoidance, and 20 neutral trials were presented in random order.

**Acquisition.** Saccades were recorded with an eye-tracking system (Eye-Trac 6; Applied Science Laboratories, Bedford, MA) that uses a corneal reflection method with bright pupil technology. The point-of-gaze is determined by the corneal reflection of an infrared beam, which is projected to the center of the illuminated pupil that rotates with each eye movement. Visual stimuli were displayed on a computer monitor using E-Prime software (Psychology Software Tools, Pittsburgh, PA).

In a darkened room and facing the stimulus monitor, participants remained comfortably seated at 60 cm from the monitor center. Prior to the eye-tracking session, a 9-point calibration was performed. Standardized instructions were carefully provided by trained personnel, and recording began after the participants demonstrated their understanding.

**Processing.** Saccades were scored off-line using ILAB software (Northwestern University Medical School and V.A. Healthcare System, Chicago, IL) [49] and MATLAB (MathWorks, Natick, MA), which calculated the latency and accuracy of correct saccades. In each trial, the first saccade was chosen as the response. A correct response was defined as a saccade with velocity $\geq 30^\circ/s$ made toward the mirror location of the peripheral target and extended beyond a 2.5$^\circ$/visual angle from central stimulus. An incorrect response occurred when the saccade was directed toward the peripheral target and exceeded the 2.5$^\circ$/visual angle from central stimulus. Performance on each trial was checked to identify blink artifacts and eventual failures of the software that detected saccades. Trials that were excluded in the analysis were those in which eye movement latencies $< 70$ ms or there was no fixation on the central stimulus at the onset of the trial [47]. The proportion of trials excluded was similar between NW and OO participants (17.4 vs 12.4%, $p = 0.215$).

Sensitivity to incentives was assessed by behavioral variables: (a) accuracy: percentage of correct responses (raw) for each incentive type; (b) latency: ms for a correct responses in each incentive type (15); (c) adjusted accuracy: to assess the effect of incentives on accuracy controlling for differences in a baseline (neutral incentive accuracy) we subtracted the accuracy in the
reward and loss incentives from accuracy of neutral incentive divided by accuracy of neutral incentive [24].

DTI data

**Acquisition.** Studies were performed with a 3-Tesla scanner (Siemens MAGNETOM Skyra System, Siemens Healthcare, Erlangen, Germany). DTI data were acquired using a single shot echo-planar imaging (EPI) sequence (echo time \(TE = 91\) ms; repetition time \(TR = 9900\) ms; field-of-view \(FOV\): 256 mm; slices: 72, slice thickness: 2 mm; slice gap: 0 mm; 30 gradient directions with \(b = 1000\) s/mm\(^2\) and 1 with \(b = 0\) s/mm\(^2\)).

**Preprocessing.** Preprocessing was performed with FMRIB Software Library (FSL, version 5.04) [50]. The steps included eddy current correction, head motion correction, and brain masking. The diffusion tensor model was then fitted at each voxel to obtain maps of FA and mean (MD), axial (AD) and radial (RD) diffusivities.

**Tract-based spatial statistics.** Using Tract-Based Spatial Statistics (TBSS, a toolbox of FSL), we performed voxel-wise analysis [51]. Running the nonlinear registration (FNIRT), FA images were aligned to the FMRIB58_FA template and affine transformed into Montreal Neurological Institute (MNI) standard space. FA images were merged to create a mean FA image, and a skeleton (centers of all WM) was then generated. To consider only WM, a threshold of 0.2 was applied to the FA skeleton. The aligned FA map of each participant was then projected onto the skeleton. The MD, RD, and AD maps were also projected onto this skeleton.

The main parameters obtained for the DTI studies were FA, MD, AD, and RD, all of which would reflect the microstructural integrity of WM. Briefly, FA is a quantitative index of the orientation of water diffusion coherence, MD is the average rate of water diffusion, AD measures diffusivity along the primary axis (eigenvalue \(\lambda_1\)), and RD is the average diffusivity of the two minor axes (eigenvalues \(\lambda_2\) and \(\lambda_3\)), i.e., it measures diffusivity perpendicular to the major axis [27, 52].

Anthropometric measures

Trained personnel applied standardized procedures (Frankfurt position, without shoes, and wearing underwear) to measure weight to the closest 0.1 kg and height to the nearest 0.1 cm (Seca scale model 700; Hamburg, Germany). BMI was calculated as the ratio of weight (kg) divided by the square of height (m\(^2\)) and then categorized as NW (18.5 to < 25.0 m/kg\(^2\)) and OW (≥ 25.0 m/kg\(^2\)).

Data analysis

To explore differences in the incentivized antisaccade task between NW and OW groups, repeated measures analysis of variance (ANOVA) were conducted. The within-participants factor was the incentive type (reward, loss, and neutral), and the between-participants factor was group. Post hoc paired t-tests used Bonferroni correction for multiple comparisons. In FSL, general linear models were calculated to explore the interaction of incentivized antisaccade task data and DTI indices (FA, MD, RD, and AD) between groups. When there was a significant interaction we tested the linear relationship between variables in each group. Each behavioral variable of incentive sensitivity was included in the design matrix. For these procedures, we utilized non parametric permutation–based statistics with the "randomise" tool (p < 0.05) [49]. Five thousand permutations were performed, and threshold-free cluster enhancement (TFCE) was applied to correct for multiple comparisons (family-wise error-rate [FWE]) [53]. To identify the location of significant clusters, JHU ICBM-DTI-81 White-Matter Labels and the JHU White-Matter Tractography Atlas were used [54, 55]. Analyses were
adjusted for waist circumference, sex, and iron-deficiency anemia in infancy. A p value < 0.05 was considered statistically significant. Statistical analysis of incentivized antisaccade task was conducted with SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA).

Results
Background characteristics for participants are shown in Table 1. All anthropometric measures were different between groups. Of the 76 participants (22.3 ± 1.3 years), 59.2% were OW.

Incentivized antisaccade task
Accuracy. There was a main effect of incentive type (F = 6.1, p < 0.005, \( \eta^2 = 0.087 \)). The neutral incentive showed lower accuracy compared to reward (65.3 vs. 71.8%, p < 0.001) and loss avoidance (65.3 vs. 72.4%, p < 0.001) incentives. Overall, the NW group showed higher percentage of correct responses than the OW group (71.7 vs. 68.1%), but this effect was not significant (F = 3.2, p = 0.079, \( \eta^2 = 0.047 \)). There was an interaction between incentive type and

Table 1. Descriptive characteristics of the study participants.

| Background characteristics | NW (n = 31) | OW (n = 45) | p |
|----------------------------|------------|------------|---|
| Female, n (%)  \(^a\)      | 14 (45.2%) | 22 (48.9%) | 0.749 |
| Age at test (years)        | 22.6 ± 1.5 | 22.1 ± 1.1 | 0.398 |
| BMI at test (kg/m\(^2\))   | 22.5 ± 1.6 | 29.9 ± 3.3 | < 0.001 |
| Waist circumference at test (cm) | 74.7 ± 6.2 | 87.7 ± 9.5 | < 0.001 |
| Risk of metabolic complications (%)  \(^a, b\) | 0 (0%) | 9 (20%) | 0.064 |
| Formal education (years)   | 11.3 ± 1.5 | 11.7 ± 0.9 | 0.097 |
| High school graduation (%) \(^a\) | 27 (87.1%) | 42 (93.3%) | 0.355 |

Values are expressed as mean ± standard deviation. Statistical comparison with the independent sample t-test
IDA: iron-deficiency anemia; NW: normal-weight; OW: overweight
\(^a\) Chi-square test or adjusted chi-square test.
\(^b\) Waist circumference > 102 cm (male) and > 88 cm (females), World Health Organization 2008.
\(^c\) Wechsler Intelligence Scale for Children R
\(^d\) Modified Graffar index.

https://doi.org/10.1371/journal.pone.0233915.t001
group (F = 6.5, p < 0.005, η² = 0.092). The NW group presented a higher percentage of correct responses for the loss avoidance incentive compared to the OW group (Fig 2). The intra-group analyses showed lower accuracy in neutral incentive compared to reward and loss avoidance incentives in NW participants. There was similar accuracy between incentives—with lower accuracy in neutral relative to reward incentive (p = 0.07)—in OW participants (Fig 2).

**Latency.** There was a suggestive longer latency for loss avoidance incentive relative to reward (438.4.5 vs. 427.8 ms, p = 0.07) and neutral (438.4 vs. 427.6 ms, p = 0.08), but the incentive-type effect was non-significant (F = 3.7, p = 0.06, η² = 0.047). The group effect (F = 0.2, p = 0.686, η² = 0.010) and the interaction between group and incentive (F = 1.7, p = 0.184, η² = 0.026) were non-significant.

**Adjusted accuracy.** The NW group showed greater adjusted accuracy in loss incentive compared to OW group (0.20 vs 0.03%, p = 0.036). However, the group effect (F = 1.3, p = 0.247, η² = 0.019) and the interaction between incentive type and group (F = 3.1, p = 0.06, η² = 0.052) were non-significant.

### Relationship between WM microstructure and the incentivized antisaccade task in NW and OW groups
The relationship between WM indices (FA, MD, AD, and RD) and incentive sensitivity (behavioral variables of the incentivized antisaccade task) was compared between NW and OW participants. The association between FA and loss avoidance accuracy differed between

---

**Fig 2. Incentivized antisaccade task accuracy between Normal-Weight (NW) and OverWeight (OW) groups.** Values are expressed as mean ± standard error. Statistical analysis was performed with repeated measures analysis of variance; * p < 0.05 ** p < 0.005.

https://doi.org/10.1371/journal.pone.0233915.g002
groups (p < 0.05; Table 2 and Fig 3). Clusters of right WM tracts that showed increasing FA values regarding the loss avoidance accuracy improvement were apparent only for the NW group (p < 0.05; Table 3 and Fig 4). For the OW group, the corresponding correlations were far from statistical significance (p = 0.10; Fig 5). Non-significant results were found for MD, AD, and RD.

**Discussion**

This study provided evidence for differences in behavioral sensitivity to incentives according to BMI categories in young adults. The NW group exhibited higher accuracy in the loss incentive compared to the OW group. In addition, the DTI results showed that higher FA values were related to enhanced loss avoidance accuracy in NW participants. The WM tracts that were related to loss sensitivity were: external capsule, superior and posterior corona radiate, superior and inferior longitudinal fasciculus, fornix, inferior fronto-occipital fasciculus, anterior and posterior thalamic radiation, posterior thalamic radiation, retrolenticular part of internal capsule, and corticospinal tract.

**Sensitivity to incentives**

Accuracy results in the NW group were lower in neutral compared to loss and reward incentives. These results are consistent with data that showed a close relationship between cognitive control and incentive type-related performance [14, 15, 17, 56]. Accuracy in the OW group was similar in all incentive types; this finding suggests that incentive itself might not have triggered the expected motivation to perform the task. We suggest that OW participants could have been more engaged with the reward incentive compared to loss incentive and probably did not identify the neutral stimuli as free of incentive [17, 24].

Compared with the NW group, the accuracy (raw and adjusted) were lower in the OW group only for the loss avoidance incentive. Previous evidence showed that potential gains generate an increase in attentional network activity only when required, whereas potential losses result in an overall and sustained increase of this network activity [56]. Thus, the correct performance in loss avoidance may be more challenging and difficult to achieve [17]. Besides, loss incentive appears to involve an emotional component above the reward incentive [17, 22, 57]. Taken together, lower accuracy in OW participants may relate to altered cognitive and emotional controls, making it tough for them to deal with this incentive type. Indeed, in a previous study from our group [16], we reported differences in accuracy for loss incentive between OW and NW adolescents. Lindgren et al. identified dopaminergic signaling disruptions in obesity [58], which may contribute to alterations in the incentive sensitivity and WM

| Cluster | White matter tracts | Cluster size (voxels) | MNI coordinates of the peak voxel | Z score |
|---------|---------------------|-----------------------|----------------------------------|--------|
| 1       | Superior corona radiata R | 334                   | 27, -16, 14                      | 0.048  |
|         | External capsule R      |                       |                                  |        |
|         | Posterior corona radiata R |                    |                                  |        |
|         | Posterior limb of internal capsule R |                |                                  |        |

Montreal Neurological Institute (MNI) template coordinates (x, y, z) and Z score refer to the voxel in the cluster with maximum probability. All brain regions were located in the right hemisphere (R). The cluster size is > 10 voxels.

https://doi.org/10.1371/journal.pone.0233915.t002
Fig 3. Interaction effect of Fractional Anisotropy (FA) and loss accuracy between groups. The red-yellow color indicates the white matter clusters that showed a significant interaction between FA and loss avoidance accuracy (at the indicated coordinates) between the normal-weight and overweight groups ($\alpha<0.05$, threshold-free cluster enhancement and family-wise error correction). The mean skeleton of FA is shown in green. Right white matter tracts include the external capsule, superior and posterior corona radiate and posterior limb of internal capsule. Coordinates are presented in Montreal Neurological Institute (MNI) template space. A: anterior; L: left.

https://doi.org/10.1371/journal.pone.0233915.g003

Table 3. White matter tracts that presented a positive linear relationship between accuracy in the loss avoidance incentive with fractional anisotropy in the normal-weight group.

| Cluster | White matter tracts | Cluster size (voxels) | MNI coordinates of the peak voxel | Z score |
|---------|---------------------|-----------------------|-----------------------------------|---------|
|         |                     |                       | x | y    | z   |          |
| 1       | External capsule R  | 2020                  | 30 | -16  | 15  | 0.026    |
|         | Superior corona radiata R |
|         | Posterior corona radiata R |
|         | Superior longitudinal fasciculus R |
|         | Inferior longitudinal fasciculus R |
|         | Fornix (cres)/Stria terminalis R |
|         | Inferior fronto-occipital fasciculus R |
|         | Anterior thalamic radiation R |
|         | Posterior thalamic radiation R |
|         | Posterior limb of internal capsule R |
|         | Sagittal striatum R |
|         | Corticospinal tract R |
|         | Retrolenticular part of internal capsule R |
|         | Cerebral peduncle R |
| 2       | Superior longitudinal fasciculus R |
|         | Inferior longitudinal fasciculus R |
|         | Retrolenticular part of internal capsule R |
| 3       | Posterior thalamic radiation R |
|         | Corticospinal tract R |
|         | Anterior thalamic radiation R |

Montreal Neurological Institute (MNI) template coordinates (x, y, z) and Z score refer to the voxel in the cluster with maximum probability. All brain regions were located in the right hemisphere (R). The cluster size is > 10 voxels.

https://doi.org/10.1371/journal.pone.0233915.t003
integrity in vulnerable brain regions [10, 59], but the direction of causality could not be established.

**Loss sensitivity and WM integrity**

In the NW group, there was a relationship between FA and accuracy in the loss avoidance incentive. The WM tracts involved in this relation have been related to the reward system, emotional regulation, and cognitive control processes. In short, (a) the external capsule—a fiber bundle that connects the cortex with the striatum—is implicated in emotion and cognitive control [40, 60]; (b) the inferior fronto-occipital fasciculus and anterior thalamic radiation...
are relevant fronto-striatal connections to the nucleus accumbens, all brain regions involved in reward and reinforcement [41, 61]; (c) the sagittal striatum and inferior longitudinal fasciculus link occipital and temporal regions with the thalamus [62] to facilitate the ability to delay gratification [63], and together with the inferior fronto-occipital fasciculus, participate in motivation to pursue new experiences [42]; (d) the superior longitudinal fasciculus—connects dorsal-frontal with inferior and superior parietal cortices—is one of the brain tracts that matures later in life, at 30–40 years [64], and assembles with corona radiata to govern attention, cognitive control, and self-regulatory functions [42, 65]; (e) the corticospinal tract converges with corona radiata and external and internal capsules [66], and their integrity plays a key role in inhibitory control modulation [33] and in reward seeking circuit [7, 67]; (f) the posterior thalamic radiation, which connects the thalamus with the cerebral cortex and basal ganglia, is relevant for cognitive control. It and the cerebral peduncle have been related with deletion of interfering information [68, 69].

Our finding that tracts of several right hemisphere regions showed significant associations with accuracy in a oculomotor task is consistent with the relationship between higher saccade inhibition performance and increased WM integrity of the right-lateralized fronto-striatal network [70], as well as with the right hemisphere dominance of the attentional network [33, 71]. The fact that the above mentioned relationships were identified only in the NW group suggests that the microstructural WM integrity of right-sided brain networks may relate to lower behavioral performance, as observed in OW participants.

Considering the results of behavioral performance and DTI, we could suggest that OW individuals may exhibit different strategies that NW subjects to reach more efficiency in cognitive control. To our knowledge, this study is one of the few that explored whether microstructural correlates of WM participate in regulating incentive sensitivity. Notably, we showed a relationship between WM tracts and task performance in NW subjects. Indeed, our findings provide new insight to explore and help understand the mechanisms that underpin brain-behavioral relationships [72].

**Limitations and strengths**

The limitations of the study include its cross-sectional nature, which precludes inferences regarding causality. Additionally, the incentivized antisaccade task did not include food-related stimuli. However, money is a powerful motivator that is widely used in human studies (24). Furthermore, because altered performances were apparent using non-food-related stimuli, our results could support a more global compromise of cognitive control in OW individuals. Another limitation is that we did not include information about healthy behaviors that can affect cognitive functions and WM composition [73]. Regarding strengths, we highlight the sample size, with a considerable number of participants in the OW group and the application of appropriate neuroimaging studies (DTI). Future studies should include additional indicators of adiposity and inflammatory factors to thoroughly identify additional differences in sensitivity to incentives and obesity-related WM alterations.

**Conclusion**

This study showed differences in behavioral sensitivity to incentives within and between groups, and that the relationship between loss sensitivity and WM integrity was closely related to BMI status. Indeed, we propose that WM integrity is relevant for brain functioning to achieve an increased performance in an incentivized antisaccade task.
Acknowledgments

We would like to express our gratitude to individuals whose participation made this study possible. We also thank technicians of the Sleep and Functional Neurobiology Laboratory of INTA, University of Chile, for their contribution during the course of this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

Author Contributions

Conceptualization: Betsy Lozoff, Bharat B. Biswal, Patricio Peirano, Cecilia Algarin.
Data curation: Sussanne Reyes, Patricio Peirano, Cecilia Algarin.
Formal analysis: Sussanne Reyes, Carolina de Medeiros Rimkus.
Funding acquisition: Sussanne Reyes, Betsy Lozoff, Patricio Peirano, Cecilia Algarin.
Investigation: Patricio Peirano.
Methodology: Sussanne Reyes, Cecilia Algarin.
Project administration: Sussanne Reyes, Patricio Peirano.
Supervision: Sussanne Reyes.
Writing – original draft: Sussanne Reyes.
Writing – review & editing: Carolina de Medeiros Rimkus, Betsy Lozoff, Bharat B. Biswal, Patricio Peirano, Cecilia Algarin.

References

1. Wang J, Yang D-L, Chen Z-Z, Gou B-F. Associations of body mass index with cancer incidence among populations, genders, and menopausal status: a systematic review and meta-analysis. Cancer Epidemiol. 2016; 42: 1–8.
2. Mandivwala T, Khalid U, Deswal A. Obesity and cardiovascular disease: a risk factor or a risk marker? Curr Atheroscler Rep. 2016; 18(5): 21.
3. Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology. 2015; 54(4): 588–600.
4. World Health Organization. Obesity and overweight [Internet]. 2018. [20 5 2019]. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
5. Ministry of Health Chile. National Health Survey: first results, 2016–17 [Internet]. 2017. [10 3 2019]. Available from: https://www.minsal.cl/wp-content/uploads/2017/11/ENS-2016-17_PRIMEROS-RESULTADOS.pdf
6. Lyn R, Heath E, Dubhashi J. Global implementation of obesity prevention policies: a review of progress, politics, and the path forward. Curr Obes Rep. 2019. https://doi.org/10.1007/s13679-019-00358-w
PMID: 31673982
7. Papageorgiou I, Astrakas LG, Xydis V, Alexiou GA, Bargiotas P, Tzarouchi L, et al. Abnormalities of brain neural circuits related to obesity: a diffusion tensor imaging study. Magn Reson Imaging. 2017; 37: 116–121.
8. Chen VCH, Liu YC, Chao SH, McIntyre RS, Cha DS, Lee Y, et al. Brain structural networks and connections: the brain–obesity interface and its impact on mental health. Neuropsy D Dis Treat. 2018; 14: 3199–3208.
9. Fandiño J, Moreira RO, Preissler C, Gaya CW, Papelbaum M, Coutinho WF, et al. Impact of binge eating disorder in the psychopathological profile of obese women. Compr Psychiatry. 2010; 51(2): 110–114.
10. Volkow ND, Wang G-J, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. Obes Rev. 2013; 14(1): 2–18.
11. Volkow ND, Wang G-J, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci. 2011; 15(1): 37–46.

12. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. Nat Rev Neurosci. 2017; 18(12): 741–752.

13. Benton D, Young HA. A meta-analysis of the relationship between brain dopamine receptors and obesity: a matter of changes in behavior rather than food addiction. Int J Obes. 2016; 40(5): S12–S21.

14. Luna B, Paulsen D, Padmanabhan A, Geier C. Cognitive control and motivation. Curr Dir Psychol Sci. 2013; 22(3): 94–100.

15. Leong JK, MacNiven KH, Samanez-Larkin GR, Knutson B. Distinct neural circuits support incentivized inhibition. NeuroImage. 2018; 178: 435–444. https://doi.org/10.1016/j.neuroimage.2018.05.056 PMID: 29803959

16. Reyes S, Peirano P, Luna B, Lozoff B, Algarín C. Potential effects of reward and loss avoidance in overweight adolescents. Pediatr Res. 2015; 78(2): 152–157.

17. Paulsen DJ, Hallquist MN, Geier CF, Luna B. Effects of incentives, age, and behavior on brain activation during inhibitory control: a longitudinal fMRI study. Dev Cogn Neurosci. 2015; 11: 105–115.

18. Verdejo-Román J, Formito A, Soriano-Mas C, Vilar-López R, Verdejo-García A. Independent functional connectivity networks underpin food and monetary reward sensitivity in excess weight. Neuroimage. 2017; 146: 293–300.

19. Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, et al. Monetary reward processing in obese individuals with and without binge eating disorder. Biol Psychiatry. 2013; 73(9): 877–886.

20. Rotge J, Poitou C, Fossati P, Aron-Wisnewsky J, Oppert J. Decision-making in obesity without eating disorders: a systematic review and meta-analysis of Iowa gambling task performances. Obes Rev. 2017; 18(8): 936–942.

21. Horstmann A, Busse FP, Mathar D, Müller K, Lepsien J, Schögl H, et al. Obesity-related differences between women and men in brain structure and goal-directed behavior. Front Hum Neurosci. 2011; 5 (58): 1–9.

22. Kube J, Mathar D, Horstmann A, Kotz SA, Villringer A, Neumann J. Altered monetary loss processing and reinforcement-based learning in individuals with obesity. Brain Imaging Behav. 2018; 12(5): 1431–1449.

23. Verdejo-Román J, Vilar-López R, Navas JF, Soriano-Ma C, Verdejo-García A. Reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. Hum Brain Mapp. 2017; 38: 666–677.

24. Geier CF, Luna B. Developmental effects of incentives on response inhibition. Child Dev. 2012; 83(4): 1262–1274.

25. Chung T, Paulsen DJ, Geier CF, Luna B, Clark DB. Regional brain activation supporting cognitive control in the context of reward is associated with treated adolescents’ marijuana problem severity at follow-up: a preliminary study. Dev Cogn Neurosci. 2015; 16: 93–100.

26. Geier CF. Adolescent cognitive control and reward processing: implications for risk taking and substance use. H orm Behav. 2013; 64(2): 333–342.

27. Kullmann S, Schweizer F, Veit R, Fritzsche A, Preisl H. Compromised white matter integrity in obesity. Obes Rev. 2015; 16: 273–281.

28. Repple J, Opel N, Meinert S, Redlich R, Hahn T, Winter NR, et al. Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts. Psychoneuroendocrinology. 2018; 91: 179–185.

29. Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesit y. 2011; 19(3): 500–504.

30. Xu J, Li Y, Lin H, Sinha R, Potenza MN. Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: a diffusion tensor imaging study. Hum Brain Mapp. 2013; 34(5): 1044–1052.

31. Kullmann S, Callaghan MF, Heni M, Weiskopf N, Scheffler K, Häring HU, et al. Specific white matter tissue microstructure changes associated with obesity. NeuroImage. 2016; 125: 36–44.

32. Lou B, Chen M, Luo X, Dai Y. Reduced right frontal fractional anisotropy correlated with early elevated plasma LDL levels in obese young adults. PLoS One. 2014; 9(10): e108180.

33. Li P, Tsapanou A, Qolamreza RR, Gazes Y. White matter integrity mediates decline in age-related inhibitory control. Behav Brain Res. 2018; 339: 249–254.

34. Hu Y, Long X, Lyu H, Zhou Y, Chen J. Alterations in white matter integrity in young adults with smartphone dependence. Front Hum Neurosci. 2017; 11: 532.
35. Birdsill AC, Oleson S, Kaur S, Pasha E, Ireton A, Tanaka H, et al. Abdominal obesity and white matter microstructure in midlife. Hum Brain Mapp. 2017; 38(7): 3337–3344.

36. Chen P, Chavez R, Heatherington T. Structural integrity between executive control and reward regions of the brain predicts body fat percentage in chronic dieters. Cogn Neurosci. 2017; 8(3): 162–166.

37. Marqués-Iturría I, Scholtens L, Garolera M, Pueyo R, García-García I, González-Tartiere P, et al. Affected connectivity organization of the reward system structure in obesity. Neuroimage. 2015; 111: 100–106.

38. Carbine KA, Duraccio KM, Hedges-Muncy A, Barnett KA, Kirwan CB, Jensen CD. White matter integrity disparities between normal-weight and overweight/obese adolescents: an automated fiber quantification tractography study. Brain Imaging Behav. 2019. https://doi.org/10.1007/s11682-019-00036-4 PMID: 30719618

39. Riederer JW, Shott ME, Deguzman M, Pryor TL, Frank GK. Understanding neuronal architecture in obesity through analysis of white matter connection strength. Front Hum Neurosci. 2016; 10: 1–8.

40. Schmahmann J, Smith E, Eichler F, Filley C. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann NY Acad Sci. 2008; 1142: 266–309.

41. Koch K, Wagner G, Schachtzabel C, Schultz CC, Güllmar D, Reichenbach JR, et al. Association between white matter fiber structure and reward-related reactivity of the ventral striatum. Hum Brain Mapp. 2014; 35(4): 1469–1476.

42. Xu J, Kober H, Carroll KM, Rounsaville BJ, Godfrey D, Potenza MN. White matter integrity and behavioral activation in healthy subjects. Hum Brain Mapp. 2012; 33(4): 994–1002.

43. Lozoff B, De Andracia I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics. 2003; 112(4): 846–854.

44. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res. 2003; 53(2): 217–223.

45. Algarín C, Nelson C a, Peirano P, Westerlund A, Reyes S, Lozoff B. Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years. Dev Med Child Neurol. 2013; 55(5): 453–458.

46. Algarín C, Karunakaran KD, Reyes S, Morales C, Lozoff B, Peirano P, et al. Differences on brain connectivity in adulthood are present in subjects with iron deficiency anemia in infancy. Front Aging Neurosci. 2017; 9: 54.

47. Geier CF, Terwilliger R, Teslovich T, Velanova K, Luna B. Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb Cortex. 2010; 20(7): 1613–1629.

48. Amador N, Schlag-Rey M, Schlag J. Reward-predicting and reward-detecting neuronal activity in the primate supplementary eye field. J Neurophysiol. 2000; 84(4): 2166–2170.
60. Chahal R, Vilgis V, Grimm KJ, Hipwell AE, Forbes EE, Keenan K, et al. Girls' pubertal development is associated with white matter microstructure in late adolescence. Neuroimage. 2018; 181: 659–669.

61. Camara E, Rodriguez-Fornells A, Ye Z, Münte TF. Reward networks in the brain as captured by connectivity measures. Front Neurosci. 2010; 3(4): 350–362.

62. Shott ME, Cornier M-A, Mittal VA, Pryor TL, Orr JM, Brown MS, et al. Orbitofrontal cortex volume and brain reward response in obesity. Int J Obes. 2015; 39(2): 214–221.

63. Olson EA, Collins PF, Hooper CJ, Muetzel R, Lim KO, Luciana M. White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: a diffusion tensor imaging study. J Cogn Neurosci. 2009; 21(7): 1406–1421.

64. Chaim TM, Zhang T, Zanetti M V, da Silva MA, Louza MR, Doshi J, et al. Multimodal magnetic resonance imaging study of treatment-naïve adults with attention-deficit/hyperactivity disorder. PLoS One. 2014; 9(10): e110199.

65. Goh S, Bansal R, Xu D, Hao X, Liu J, Peterson BS. Neuroanatomical correlates of intellectual ability across the life span. Dev Cogn Neurosci. 2011; 1(3): 305–312.

66. Waller R, Dotterer HL, Murray L, Maxwell AM, Hyde LW. White-matter tract abnormalities and antisocial behavior: a systematic review of diffusion tensor imaging studies across development. NeuroImage Clin. 2017; 14: 201–215.

67. Li W, Zhu J, Li Q, Ye J, Chen J, Liu J, et al. Brain white matter integrity in heroin addicts during methadone maintenance treatment is related to relapse propensity. Brain Behav. 2016; 6(2): e00436.

68. Cremers LGM, de Groot M, Hofman A, Krestin GP, van der Lugt A, Niessen WJ, et al. Altered tract-specific white matter microstructure is related to poorer cognitive performance: the Rotterdam Study. Neurobiol Aging. 2016; 39: 108–117.

69. Chaddock-Heyman L, Erickson KI, Voss MW, Powers JP, Knecht AM, Hillman CH, et al. White matter microstructure is associated with cognitive control in children. Biol Psychol. 2013; 94(1): 109–115.

70. Thakkar KN, van den Heiligenberg FMZ, Kahn RS, Neggers SFW. Speed of saccade execution and inhibition associated with fractional anisotropy in distinct fronto-frontal and fronto-striatal white matter pathways. Hum Brain Mapp. 2016; 37(8): 2811–2822.

71. Shulman GL, Pope DLW, Astafiev SV, McAvoy MP, Snyder AZ, Corbetta M. Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J Neurosci. 2010; 30(10): 3640–3651.

72. Bessette KL, Stevens MC. Neurocognitive pathways in attention-deficit/hyperactivity disorder and white matter microstructure. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019; 4(3): 233–242.

73. Voss M, Heo S, Prakash R, Erickson KI, Alves H, Chaddock L, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum Brain Mapp. 2013; 34(11): 2972–2985.