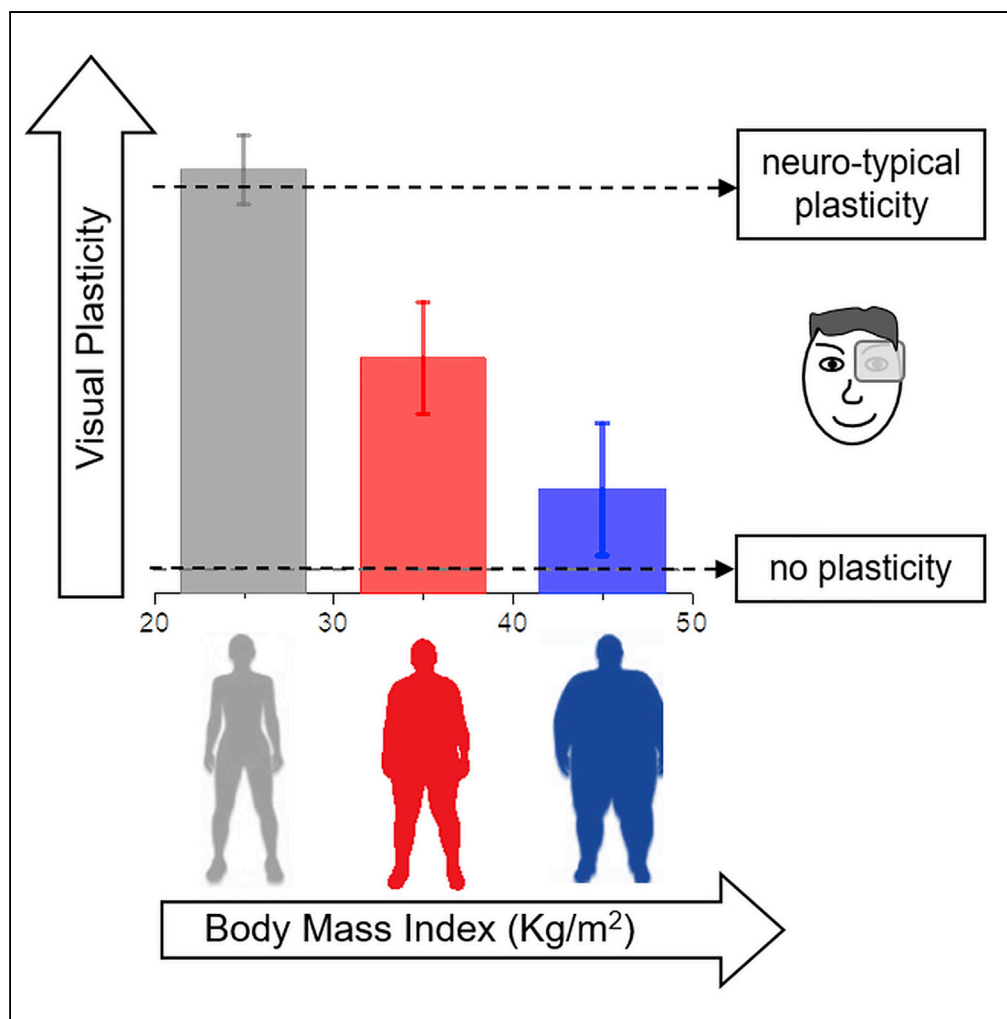**Article**

Altered Visual Plasticity in Morbidly Obese Subjects

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HIGHLIGHTS

Cognitive decline occurs
in obesity suggesting
altered high-level brain
plasticity

Low-level sensory
plasticity in adults
declines with increasing
body mass index

Morbidly obese subjects
show altered visual
plasticity and interocular
interactions

Article

Altered Visual Plasticity in Morbidly Obese Subjects

Claudia Lunghi,[1,5] Giuseppe Daniele,[2,5] Paola Binda,[3] Angela Dardano,[2] Giovanni Ceccarini,[2] Ferruccio Santini,[2] Stefano Del Prato,[2] and Maria Concetta Morrone[3,4,6,*]

SUMMARY

Growing evidence indicates a close link between energy metabolism and neural plasticity as obesity is associated with alterations of cognitive functions, memory, and hippocampal neurogenesis. However, it is still unknown whether obesity can affect low-level sensory plasticity. Here we investigated this issue by probing early visual plasticity induced by short-term (2 h) monocular deprivation in a group of adult volunteers with a wide range of Body Mass Index (BMI), from normal weight to morbid obesity. We found that the effect of monocular deprivation decreased with increasing BMI, and morbidly obese subjects (BMI>40) failed to show the homeostatic plasticity effect seen in normal-weight participants. In addition, morbidly obese subjects exhibited altered binocular rivalry dynamics compared with normal-weight observers. These results show for the first time that the impact of obesity observed at the neural and cognitive level extends to basic sensory processing and plasticity.

INTRODUCTION

Obesity is one of the recognized worldwide health issues, with an increasing prevalence in both the developed and developing countries (Di Cesare et al., 2016). Besides weight gain and metabolic diseases, obesity is also associated with deficits in high-level brain processing and function (for review Guillemot-Legris and Muccioli, 2017). This suggests an interplay between peripheral metabolism, high-level brain functions, and hippocampal plasticity. However, it is still unknown whether obesity might affect lower-level sensory functions and plasticity. To address this issue, here we investigate the degree of short-term visual cortex plasticity in a group of healthy adult individuals belonging to different body weight categories, ranging from normal weight to morbid obesity.

Similar to previous studies on short-term visual plasticity, we quantified sensory eye dominance by means of binocular rivalry, a form of bistability that occurs when the two retinae are presented with dissimilar visual stimuli (Alais and Blake, 2005; Levelt, 1965). Normally, eye dominance is relatively balanced between the two eyes; however, after short-term (2 h to 2 h 30 min) monocular deprivation, eye dominance dramatically shifts in favor of the deprived eye (Lunghi et al., 2011). The deprivation effect usually decays within 1 h after eye-patch removal (but see Lunghi et al., 2013) and is thought to reflect a form of homeostatic plasticity. Homeostatic plasticity has been observed during development in animal models (Turrigiano and Nelson, 2004; Mrsic-Flogel et al., 2007; Maffei et al., 2010; Turrigiano, 2012) and in children during the critical period for binocularity (Lunghi et al., 2016) and is partially preserved in adult age (for a detailed discussion see Binda et al., 2018). It has been shown that this form of short-term plasticity is accompanied by transient changes of neuronal excitability in V1 (Begum and Ts'o, 2016; Binda et al., 2018; Lunghi et al., 2015a) and by a decrease of GABA measured by MR spectroscopy (Lunghi et al., 2015b). Thus, the demonstration of a change of homeostatic plasticity in obesity may provide strong evidence of the link between energy metabolism and basic sensory brain mechanisms.

RESULTS

We measured the effect of short-term (2 h) monocular deprivation on sensory eye dominance by binocular rivalry on a group (N = 53) of adult healthy individuals with a wide range of body weight, from normal weight to morbid obesity. To avoid other potential factors that may also affect neuronal plasticity, we have included in the study only subjects with normal glucose tolerance. We computed the Body Mass Index (BMI) using the standard equation described in Equation 1 in the Transparent Methods section (Table 1). The ocular dominance plasticity was evaluated by the difference between sensory eye dominance (see Equation 2 in the Transparent Methods section) measured after and before 2 h of monocular deprivation (Figure 1A).

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Subject ID	Gender	Age (years)	BMI
S1	F	41	41.27
S2	F	41	51.03
S3	F	33	48.12
S4	F	55	48.44
S5	F	48	39.26
S6	F	31	36.48
S7	F	38	37.64
S10	F	27	50.07
S11	M	43	52.85
S12	F	25	46.3
S13	F	29	31.6
S14	F	38	36.3
S15	M	25	50.52
S16	F	48	39
S17	F	49	40.5
S18	F	27	47.89
S19	F	55	40.86
S20	M	48	53.49
S21	F	38	30.94
S22	M	53	26.78
S23	M	44	24.07
C1	F	25	22.52
C2	F	31	21.875
C3	F	23	18.81
C4	F	24	20.02
C5	M	20	22.15
C6	F	43	19.53
C7	M	21	25.53
C8	M	22	19.37
C9	F	21	20.06
C10	F	20	18.81
C11	F	20	24.89
C12	M	29	22.79
C13	F	20	19.13
C14	M	19	21.43

Table 1. Subjects Demographics and Body Mass Index (BMI) Values

Subject ID	Gender	Age (years)	BMI
C15	F	20	19.19
C16	F	20	18.75
C17	M	21	23.45
C18	F	20	25.7
S24	F	45	45.33
S25	F	53	41.37
S26	F	53	31.59
S27	F	50	32.51
S28	F	45	45.17
S29	F	22	31.34
S30	F	46	39.33
S31	M	47	42.24
S32	F	48	35.57
S33	M	41	37.35
S34	F	26	45.36
S35	M	20	38.77
S36	F	52	32.62
S37	M	36	38.6

Table 1. Continued

The plasticity effect of monocular deprivation reduced significantly with increasing BMI (Figure 1B), as revealed by a univariate ANOVA ($F_{(2,50)}$ = 10.27, $p < 0.001$, η^2 = 0.29) and confirmed by the strong correlation across subjects between the plasticity effect and BMI (Pearson's r = -0.58 [95% confidence interval (CI), −0.74 to −0.37], $p < 0.001$). When grouping the subjects in three categories according to their BMI, in normal to overweight subjects (group 1) we observed a significant shift of ocular dominance in favor of the deprived eye after deprivation (deprivation effect [mean $\pm$ SD] = 0.12 $\pm$ 0.05, t(19) = 11.6, $p < 0.001$), in line with previous reports (Binda and Lunghi, 2017; Lunghi et al., 2013, 2011). In subjects with moderate to severe obesity (group 2), the effect of deprivation was significantly smaller (t(34) = 3, p = 0.03) but still statistically different from 0 (mean $\pm$ SD = 0.07 $\pm$ 0.07, t(15) = 3.81, p = 0.01), whereas in morbidly obese subjects (group 3) sensory eye dominance did not change after monocular deprivation (mean $\pm$ SD = 0.02 $\pm$ 0.08, t(16) = 1.21, p = 0.99). The plasticity effect was significantly different between group 1 (normal to overweight) and group 3 (morbidly obese, t(35) = 4.46, $p < 0.001$), whereas there was no statistical difference between the two groups of obese patients (group 2 and 3, t(32) = 1.5, p = 0.86), indicating altered short-term visual plasticity in obese subjects.

A complementary measure of inter-ocular suppression is given by the proportion of time in which fusion of the two monocular images is perceived, usually referred to as mixed percepts. Strong fusion of inconsistent images is associated with weak inter-ocular inhibition (Klink et al., 2010; Robertson et al., 2015; Said and Heeger, 2013). We found that the proportion of mixed percepts remained similar before and after deprivation in both group 1 and group 2, whereas it showed a reduction in morbidly obese subjects (group 3, paired-samples t test, t(16) = 5.99, $p < 0.001$). Importantly, we also found that the proportion of mixed percepts before deprivation is related to and increases with increasing BMI (Figure 1C). This was revealed by a univariate ANOVA ($F_{(2,50)}$ = 7.47, p = 0.001, η^2 = 0.23) and confirmed by the correlation across subjects between the proportion of mixed percepts and BMI (Pearson's r = 0.45 [95% CI, 0.21 to 0.64], p = 0.004). Post hoc tests showed that the proportion of mixed percepts was significantly larger in morbidly obese subjects (group 3) compared with normal to overweight subjects (t(35) = 3.86, $p < 0.001$), whereas there was no
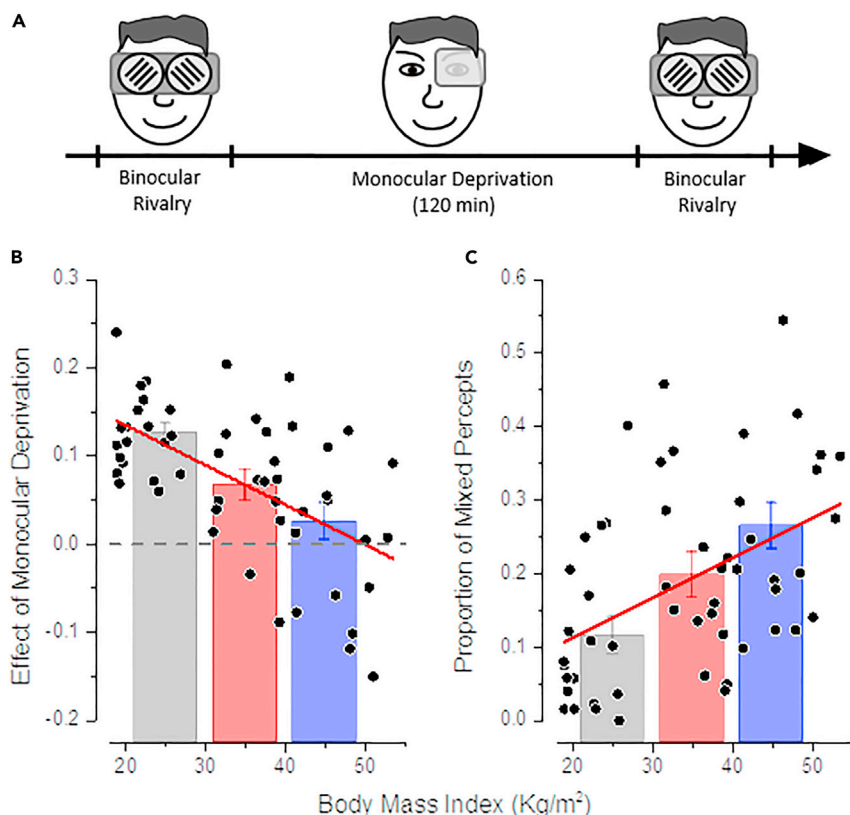
Figure 1. Short-term Monocular Deprivation Effect and Binocular Rivalry Dynamics as a Function of BMI

(A) Diagram of the experimental paradigm.

(B) The effect of monocular deprivation (difference between ocular dominance measured after and before 2 h of monocular deprivation) plotted as a function of subjects' Body Mass Index (BMI). The bars represent the average effect for three different BMI categories (gray, normal to overweight; red, obese class I and II; blue, obese class III), error bars represent 1 $\pm$ SEM. Black symbols represent single subjects' data.

(C) Same as (B) but for the proportion of the total time of mixed percepts measured during binocular rivalry before monocular deprivation.

difference in mixed percepts proportion between moderately to severely obese subjects (group2) and either group 1 (t(34) = 2.16, p = 0.11) or group 3 (t(32) = 1.5, p = 0.39). Similar results were observed for the mean duration of mixed percepts that varied from 1.81 $\pm$ 0.24 s in normal-weight subjects to 2.93 $\pm$ 0.41 s in morbidly obese subjects, suggesting that the mean duration of mix percept varied with BMI (univariate ANOVA F(2,50) = 3.89, p = 0.027, η^2 = 0.14, correlation Pearson's r = 0.27 [95% CI, −0.01 to 0.5], p = 0.05).

No difference across body weight categories was observed for the other main parameter of binocular rivalry dynamics: mean phase durations were comparable across groups (univariate ANOVA [F(2,50) = 0.85, p = 0.44, η^2 = 0.03], group1 mean $\pm$ SD = 3.5 $\pm$ 1.4, group2 mean $\pm$ SD = 4.2 $\pm$ 1.5, group3 mean $\pm$ SD = 3.8 $\pm$ 1.5). We also found a correlation between BMI and age (Pearson's r = 0.49 [95% CI, 0.25 to 0.67], p = 0.001, Bayes Factor [BF] = 94.1), as obese subjects were on average older than normal to overweight subjects. However, age did not correlate significantly with the effect of monocular deprivation (Pearson's r = −0.3 [95% CI, −0.53 to −0.08], p = 0.017, BF = 1.19). To disentangle the contribution of different factors (BMI, proportion of mix percepts and age) to the observed plasticity effect, we performed a multiple linear regression analysis using the three factors mentioned earlier as predictors of the deprivation effect. The analysis revealed that only the factor BMI was a significant predictor of the plasticity effect (t = −3.8, p < 0.001); both the factor proportion of mixed percepts (t = −1.9, p = 0.064) and the factor age (t = 0.17, p = 0.87) had no significant predictive value, implying that the apparently negative correlation between the effect of deprivation and the proportion of mixed percepts is a by-product of the correlation between both variables and BMI.
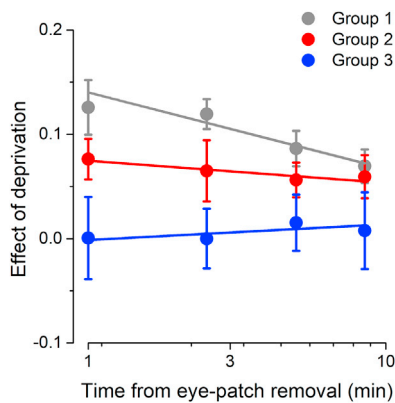
Figure 2. Decay of the Effect of Monocular Deprivation across Different BMI Groups

The effect of monocular deprivation is plotted for each of the four experimental blocks acquired after eye-patch removal and for the three different BMI groups (black symbols, normal weight to overweight subjects; red symbols, class I and class II obese subjects; blue symbols, class III obese subjects). Error bars represent $1 \pm$ SEM.

We asked whether the lack of short-term plasticity in morbidly obese subjects could result from a different dynamics of the effect—perhaps a faster decay. Figure 2 shows the decay of the plasticity effect (shift in ocular dominance) over the four experimental blocks acquired immediately after eye-patch removal. Ever since the first time point after eye-patch removal, morbidly obese subjects fail to show the ocular dominance shift, suggesting a total lack of effect after 2 h of monocular deprivation. A mixed model ANOVA (within-subjects factor TIME and the between subjects factor BMI GROUP) showed that there was no significant difference in the decay of the effect of deprivation: the interaction between the factors TIME and BMI GROUP was not significant ($F_{(6,147)} = 0.45$, $p = 0.85$, $\eta^2 = 0.02$).

Finally, the effect of monocular deprivation might be masked by strong natural ocular dominance. This potential confound is particularly important since we always deprived the dominant eye, which gives the largest deprivation effects in typical subject (Lunghi et al., 2011). However, we found that natural ocular dominance was not systematically different in morbidly obese subjects (Figure 3). The ocular dominance index measured before deprivation did not differ across BMI groups (univariate ANOVA, $F_{(2,50)} = 0.34$, $p = 0.71$, $\eta^2 = 0.01$), nor did it correlate with BMI across subjects (Pearson's $r = 0.12$, $p = 0.43$).

DISCUSSION

We found that the degree of residual homeostatic visual plasticity and binocular rivalry dynamics were altered in morbidly obese adult subjects. Both homeostatic plasticity (Binda et al., 2018; Lunghi et al., 2015a) and binocular rivalry (Lee et al., 2007; Leopold and Logothetis, 1996) occur at the earliest stages of visual processing, at the level of the primary visual cortex. Interestingly, homeostatic plasticity (Lunghi et al., 2015b) and binocular rivalry dynamics (Mentch et al., 2019; Robertson et al., 2015; van Loon et al., 2013) are both mediated by GABAergic inhibition, suggesting that intracortical excitation/inhibition balance might be altered in obese individuals in favor of a stronger GABAergic inhibition.

Experiments on animal models demonstrated that homeostatic plasticity is a particular form of experience-dependent plasticity that operates during the critical period to shape organization of binocular mechanisms in primary visual cortex (Turrigiano and Nelson, 2004). Both homeostatic plasticity (Maffei et al., 2010) and long-term plasticity (Fagiolini and Hensch, 2000), mainly relying on Hebbian cellular mechanisms (Cooke and Bear, 2014), depend on the net excitation/inhibition ratio in the visual cortex, which changes dramatically during the critical period for visual development. Thus, in spite of being different mechanisms (for discussion see Binda et al., 2018), these two forms of plasticity may be expected to co-vary in many pathological conditions that modify the excitatory/inhibitory homeostasis. Interestingly, an example of correlation between the two forms of plasticity has been observed in amblyopic children, where homeostatic plasticity is a predictive measure of the recovery of visual acuity in the amblyopic eye after standard occlusion therapy (Lunghi et al., 2016). Another example of interaction between the two forms of plasticity is provided by the long-term recovery of visual acuity in adult amblyopic subject after inducing repetitively homeostatic plasticity (Lunghi et al., 2019; Zhou et al., 2019). So, although the effect reported here is transient, a large corpus of the literature on animal models and humans suggests that homeostatic plasticity may be an important biomarker of the brain's ability to respond to environmental changes (Turrigiano, 2017).
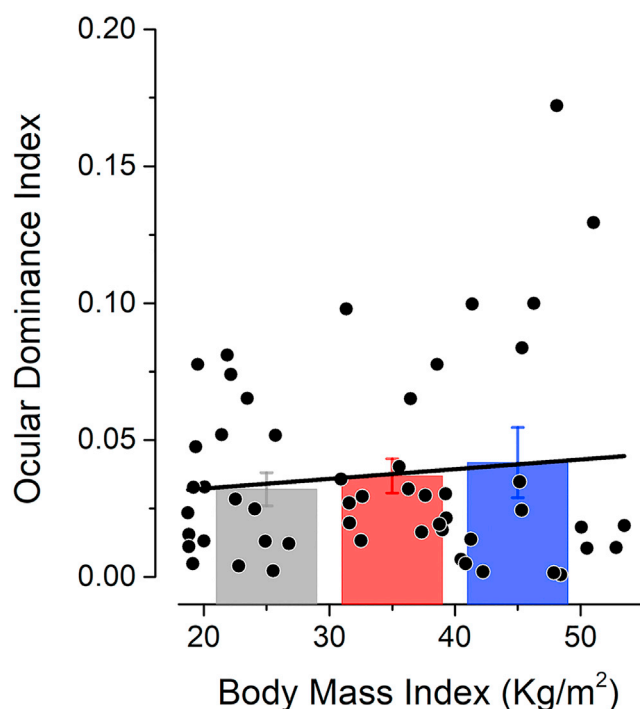
Figure 3. Ocular Dominance as a Function of BMI

The ocular dominance index measured before deprivation is plotted as a function of subjects' BMI. Individual subjects are represented by black symbols. Average ocular dominance values for each BMI group are represented by the bars (same color code as in Figure 2). Error bars represent 1 $\pm$ SEM.

Here we find that, morbidly obese subjects not only fail to show homeostatic plasticity for ocular dominance, but also have a different dynamics of binocular rivalry. The period of fusion of the two inconsistent monocular stimuli is longer than in normal-weight subjects, suggesting a decrease of interocular inhibition (Klink et al., 2010; Robertson et al., 2015; Said and Heeger, 2013). At first sight, this result seems to contradict the conclusion of increased GABAergic inhibition in obese patients, based on the lack of homeostatic ocular dominance shift after deprivation. However, a recent study (Mentch et al., 2019) showed that the duration of mixed percepts and that of exclusive dominance during binocular rivalry are modulated differently by GABA-A and GABA-B agonists, suggesting that the two measures may reflect independent inhibitory mechanisms that are both atypical in morbidly obese subjects. In addition, this population shows an atypical reduction of mixed percept after deprivation, not observed in normal-weight subjects, and in contrast with the result of a recent study (Sheynin et al., 2019). These authors classified mixed percept on a finer scale, estimating separately the mixed percepts with a relative dominance for either eye. They found that the balanced mixed percepts showed no change, consistently with our results in normal-weight individuals. Overall, morbidly obese individuals have alterations of three properties of binocular rivalry (baseline mixed percepts, the deprivation effect on ocular dominance, and its effect on mixed percepts), implicating abnormal interocular interactions.

Growing evidence indicates that obesity is not only associated with metabolic diseases, but also affects high-level brain processing and function. Morbidly obese subjects are more liable to develop neurodegenerative diseases such as Alzheimer and Parkinson disease (Mazon et al., 2017). At the functional level, it has been shown that obese individuals have impaired cognitive and executive functions, reduced spatial and recognition memory, impaired spatial learning and altered temporal integration (Scarpina et al., 2016). At the neural level, obesity is associated with severe neuroinflammation, reduced gray and white matter volume, damage in the hippocampus (reduced volume and hippocampal neurogenesis), structural changes in the frontal and temporal lobe, and altered connectivity and dopamine release in the neural circuits related to reward processing (reviewed in Guillemot-Legris and Muccioli, 2017; Matikainen-Ankney and Kravitz, 2018; Stice and Burger, 2019). Our results suggest that similar mechanisms might mediate ocular dominance plasticity. Interestingly, it has been shown that neuroinflammation induced by obesity can be

mended by physical exercise. We have recently reported that visual homeostatic plasticity can be boosted by physical exercise both in normal sighted (Lunghi and Sale, 2015) and in amblyopic subjects (Lunghi et al., 2019). Therefore, we hypothesize that reduced physical activity can contribute to the loss of homeostatic plasticity in obese individuals, although it may be difficult to disentangle the two factors. However, both explanations strongly point to a role of body metabolism in mediating visual plasticity.

Our results indicate that both early sensory plasticity and visual processing are altered in non-diabetic obese individuals, showing for the first time that the deficits observed both at the neural and functional level for higher cognitive functions extend to basic sensory processing.

Limitations of the Study

One limitation of the current study is the relatively small sample size due to the difficulty of recruiting morbidly obese individuals without associated metabolic conditions.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2019.11.027.

AUTHOR CONTRIBUTIONS

C.L., G.D., M.C.M., and S.D.P. designed the experiment; G.D., A.D., G.C., and F.S. recruited the patients and performed clinical examinations; C.L. and P.B. collected and analyzed the data; C.L., G.D., P.B., S.D.P., and M.C.M. discussed the results and wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental Information

Altered Visual Plasticity

in Morbidly Obese Subjects

Claudia Lunghi, Giuseppe Daniele, Paola Binda, Angela Dardano, Giovanni Ceccarini, Ferruccio Santini, Stefano Del Prato, and Maria Concetta Morrone

Transparent Methods

Subjects

A group of 53 adult volunteers (15 males, age: mean ± SD = 35±12 years, range from 18 to 55 years), participated in the study. All subjects had normal or corrected-to-normal visual acuity. For each subject, body weight and height were measured in order to compute the Body Mass Index (BMI). The average (mean±SD) BMI was 34±11 (range: from 18.75 to 53.5). Subjects data are reported in Table 1. All obese subjects (BMI>30) underwent a full metabolic assessment and only subjects with normal glucose tolerance were included in the study. Morbidly obese subjects (BMI>40) also underwent a battery of cognitive tests (Mini Mental State Examination and Montreal Cognitive Assessment), all subjects showed cognitive performances in the normal range. Subjects with psychiatric disorders, neurodegenerative diseases, epilepsy, depression treatment, steroids treatment, traumatic brain injury over the preceding six months, liver function enzymes higher more than two times the upper limit, heart failure (NYHA III-IV), type 1 diabetes and women who were pregnant or breastfeeding were excluded from the study.

Ethics Statement

All subjects gave informed consent to participate to the study, which adhered to the tenets of the Declaration of Helsinki and was approved by the local ethical committee [Comitato Etico Pediatrico Regionale—Azienda Ospedaliero-Universitaria Meyer—Firenze (FI)], under the protocol "Plasticità del sistema visivo" (3/2011).

Apparatus and stimuli

The experiment took place in a dark and quiet room at the Unit of Metabolic Diseases and Diabetes of the clinical hospital of Pisa (Azienda Ospedaliero-Universitaria Pisana).

Visual stimuli were generated by the VSG 2/5 stimulus generator (CRS, Cambridge Research Systems), housed in Laptop (Dell) controlled by Matlab programs. Visual stimuli were two sinusoidal gratings, oriented either 45° clockwise or counterclockwise (size: 2σ = 2°, spatial frequency: 2 cpd), presented on a uniform background (luminance: 9cd/m2 CIE x=.311, y=.341) in central vision with a central black fixation point and a common squared frame to facilitate dichoptic fusion. Visual stimuli were displayed on a 17-inch CRT monitor (FD Trinitron CRT multiscan G200) monitor, driven at a resolution of 1024x600 pixels, with a refresh rate of 120 Hz. Observers viewed the display at a distance of 57 cm through CRS Ferro-Magnetic shutter goggles that occluded alternately one of the two eyes each frame. Responses were recorded through the computer keyboard.

Procedures

Monocular Deprivation

Monocular deprivation was performed using an eye-patch of a translucent plastic material that allowed light to reach the retina (luminance attenuation 0.07 logUnits) but completely prevented pattern vision, as assessed by the Fourier transform of a natural world image seen through the eye-patch. The dominant eye (the eye showing longer perceptual predominance in binocular rivalry and/or the fixation eye at the Porta test) was patched for two hours. During the 2h of monocular occlusion patients were free to perform normal activities (walking, reading, using a computer).

Binocular Rivalry

Each binocular rivalry experimental block lasted 125 seconds. After an acoustic signal (beep), the binocular rivalry stimuli appeared. Subjects reported their perception (clockwise, counterclockwise or mixed) by continuously pressing with the right hand one of three keys (left, right and down arrows) of the computer keyboard. At each experimental block, the orientation associated to each eye was randomly varied so that neither subject nor experimenter knew which stimulus was associated with which eye until the end of the

session, when it was verified visually. Two binocular rivalry experimental blocks were acquired before short-term monocular deprivation and four blocks after eye-patch removal.

Analyses

The Body Mass Index (BMI) was computed for each subject using the following (standard) equation:

$$\frac{\text{Weight(Kg)}}{\text{Height(m)}^2}$$

Eq.1

The perceptual reports recorded through the computer keyboard were analyzed using Matlab. Mean phase durations for the two orientations and for mixed percepts (the average perceptual duration of each rivalrous stimulus) as well as the total time (T) spent by the observer perceiving the stimulus presented to either eye (deprived and non-deprived) and the total time of mixed percepts were computed. Proportion of mixed percept is the total time of mixed percept normalized by total trial time (T).

To quantify sensory eye dominance, we obtained an index of ocular dominance, ranging from 0 (complete dominance of the non-deprived eye) to 1 (complete dominance of the deprived eye), according to the following equation:

$$\frac{T_{Dep}}{T_{Dep} + T_{NonDep}}$$

Eq.2

The effect of monocular deprivation was computed as the difference between the sensory eye dominance index measured after and before the 2h of monocular deprivation. This measure was not affected by the variation in proportion of the mixed percept.

Statistics

Statistical analyses were performed using SPSS-2.0 and Matlab software. Subjects were divided into three groups according to their BMI: group 1 (N=20) included healthy-weight (N=17, BMI range from 18.5 to 25) and overweight subjects (N=3, BMI range from 25.1 to 30), group 2 (N=16) included class I (BMI range from 30.1 to 35) and class II (BMI range from 35.1: to 40) obese subjects (moderate and severe obesity) and group 3 (N=17) included class III (BMI > 40.1) obese subjects (morbid obesity). The effect of monocular deprivation and the proportion of mixed percepts were then compared across groups using a univariate ANOVA. Post-hoc tests were performed by using independent-samples t-tests, the obtained p-value was corrected for multiple comparisons using the Bonferroni method. All t-tests were two-tailed and α value was fixed at 0.05.

The sample size was determined based on previous studies measuring the effect of short-term monocular deprivation on ocular dominance in adult humans (Binda and Lunghi, 2017; Lunghi et al., 2015a, 2013, 2011). These studies showed that a sample size between 10 and 20 provides enough power to reveal the effect of short-term monocular deprivation.

Correlations were computed using the Pearson's correlation coefficient (r), statistical significance assessed using a permutation test. The obtained p-value was corrected for multiple comparisons using the Bonferroni method. In order to assess the robustness of the correlation, we also computed the Bayes Factor (BF): conventionally, a BF lower than 0.3 indicates evidence in favor of the null hypothesis (no correlation), whereas a BF larger than 3 indicates evidence in favor of the alternative hypothesis and therefore a robust correlation between the two variables tested.