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1 **Bariatric Surgery Restores Visual Cortical Plasticity in Non-Diabetic Subjects with Obesity**

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45 **Abstract**

46
47 **Background/Objectives:** Obesity leads to changes in synaptic plasticity. We aimed at investigating the
48 impact of bariatric surgery (RYGB) on visual neural plasticity (NP) and its relationship with the main
49 gut peptides, leptin, and brain-derived neurotrophic factor (BDNF).

50 **Subjects/Methods:** NP was assessed testing binocular rivalry before and after 2h of monocular
51 deprivation (index of visual brain plasticity) in 15 subjects with obesity (age 42.3 ± 9.8 years; BMI
52 46.1 ± 4.9 kg/m²) before and after RYGB. Gut peptides, leptin and BDNF were obtained at baseline and
53 six months after surgery in 13 subjects.

54 **Results:** a significant reduction in BMI ($p < 0.001$ vs baseline) and a significant increase of disposition
55 index (DI, $p = 0.02$ vs baseline) were observed after RYGB. Total and active GLP-1 release in response
56 to glucose ingestion significantly increased after RYGB, while no changes occurred in VIP, GIP and
57 BDNF levels. Fasting leptin concentration was lower after RYGB ($p = 0.001$ vs baseline). Following
58 RYGB, NP was progressively restored ($p < 0.002$). NP was correlated with DI and fasting Glucose at
59 baseline ($r = 0.75$, $p = 0.01$; $r = -0.7$, $p = 0.02$; respectively), but not with BMI. A positive correlation
60 between post-pre RYGB changes in $AUC_{\text{active GLP-1}}$ and NP was observed ($r = 0.70$, $p < 0.01$). Leptin was
61 inversely correlated with NP six months after surgery ($r = -0.63$, $p = 0.02$). No correlation was observed
62 between GIP, VIP, BDNF and NP.

63 **Conclusions:** Visual plasticity is altered in subjects with obesity, and it can be restored after RYGB.
64 The improvement may be mediated by amelioration of insulin sensitivity, increased GLP-1 levels and
65 reduced leptin levels.

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72 **Introduction**

73 The worldwide dramatic increase of the prevalence of obesity is generating major health concerns
74 because of the severe comorbidities accompanying this condition (1). Among them, cognitive
75 dysfunction and neurodegenerative diseases have been recently drawn growing attention (2). The
76 negative impact of obesity on the central nervous system is supported by studies of magnetic resonance
77 imaging (MRI) that have identified lacunar infarcts, white matter hyperintensities, and brain atrophy
78 (3). These anatomic alterations are suggested to be a consequence of the metabolic disturbances, insulin
79 resistance, abnormalities in the signaling of gut hormones and adipokines on the brain (4). Peripheral
80 insulin resistance is a common feature in obesity and recent studies have suggested that impaired
81 insulin action may occur in the brain as well (5). Insulin receptors are widespread in the hippocampal
82 and cortical brain structures, and brain insulin resistance may contribute to the cognitive impairment
83 and neurodegeneration observed in obesity (6). Insulin can regulate neuronal survival and metabolism
84 through modulation of gamma-aminobutyric acid (GABA) and glutamate receptors in the hippocampus
85 and motor cortex, structures involved in learning and memory functions (7).

86 Weight loss, as it can be obtained with bariatric surgery, has been shown to exert beneficial effects on
87 both brain structure and function (8). Body weight reduction has been associated with enhanced
88 activity in neural circuits in areas involved in executive control, such as the dorsolateral prefrontal
89 cortex (9), the superior frontal gyri and the posterior cingulate cortex (10). Bariatric surgery does not
90 simply lead to significant body weight reduction, but it is also associated with changes in incretins and
91 adipokines (11). They are key elements of the gut-brain axis, a multidirectional communication system
92 linking the enteric nervous system and the central nervous system via endocrine signals, such as
93 Glucagon-Like Peptide 1 (GLP-1), Glucose-dependent insulintropic polypeptide (GIP) and Vasoactive
94 Intestinal Peptide (VIP), and the activation of the enteric nervous system and vagal signaling (12). In
95 keeping with an effect of GLP-1 on brain function, we have recently shown that exenatide
96 administration can modulate cerebral glucose metabolic rate in several cortical and sub-cortical areas

97 (13) along with modulation of visual responses to food and non-food images in non-diabetic subjects
98 with obesity undergoing functional MRI (fMRI) (14). White adipose tissue, the body's energy depot, is
99 also connected with the central nervous system through leptin signaling. Leptin receptors are
100 widespread in the brain (e.g., throughout the cortex and the hippocampus) and their activation is
101 implicated in memory processes (15). Leptin has also been shown to exert neuroprotective functions by
102 inhibiting apoptosis and improving cell survival through regulation of apoptotic enzymes and activation
103 of neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) (16). However, it is still
104 unknown whether bariatric surgery can impact on one of the fundamental properties of the brain: the
105 ability to modify its connection or rewire in response to experience, a phenomenon known as neural
106 plasticity (17).

107 We have recently reported (18) that a particular form of neural plasticity (visual homeostatic plasticity
108 of ocular dominance) is severely blunted in subjects with BMI >40 Kg/m². In normal weight adult
109 subjects, a short period of monocular deprivation transiently shifts ocular dominance in favor of the
110 deprived eye both at the perceptual (19,20,21,22) and at the neural level (23,24) reflecting a
111 compensatory regulation of ocular dominance in response to deprivation consistent with homeostatic
112 plasticity (25) We have shown that a strong correlation exists between body mass index (BMI) and this
113 form of visual plasticity (18): the effect of short-term monocular deprivation declines with increasing
114 BMI and is completely absent in subjects with morbidly obesity. Here, we investigate the impact of
115 bariatric surgery on early sensory plasticity and the role of main circulating gut hormones and
116 adipokines in patients with obesity by measuring the effect of short-term monocular deprivation on
117 ocular dominance before and after bariatric surgery.

118

119 **Subjects and Methods**

120 *Participants and Recruitment*

121 Subjects with obesity candidate for Roux-en-Y gastric bypass (RYGB) were screened for enrollment at
122 the Obesity Centre of the Azienda-Ospedaliero Universitaria Pisana, Pisa, Italy. Subjects with age 18-

123 60 years, BMI >35 kg/m², HbA1c <6.5% and eGFR >60 ml/min/1.73m² were considered eligible.

124 Individuals with the following conditions were excluded from the study:

- 125 • psychiatric disorders
- 126 • mental retardation
- 127 • severe cognitive impairment
- 128 • neurodegenerative diseases
- 129 • epilepsy
- 130 • steroid treatment
- 131 • traumatic brain injury over the preceding six months
- 132 • liver function enzymes higher than twice the upper limit
- 133 • heart failure (NYHA III-IV)
- 134 • overt Type 2 and Type 1 diabetes
- 135 • pregnant or breastfeeding women
- 136 • history or current evidence of any condition, therapy, laboratory abnormality or other
- 137 circumstances which, in the opinion of the investigators, were deemed to expose the patient to
- 138 an unacceptable risk or could interfere with trial procedures

139 The study has been registered at ClinicalTrials.gov (NCT03414333) and the study protocol was
140 approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki
141 (2008). Each participant provided written informed consent before entering the study.

142 A total of 15 subjects (Age: 42.3 ± 9.8 years, BMI: 46.1±4.9 Kg/m²) were included in the study. All had
143 normal or corrected to normal visual acuity and no visual deficits. Two participants chose not to
144 complete the oral glucose level test; for these participants, only the neural plasticity results are
145 available.

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149 ***Study Design***

150 At baseline, participants underwent two visits (V1 and V2) at 5-14-day interval. In V1 brain plasticity
151 of the visual cortex was measured in fasting condition through a psychophysical technique based on the
152 binocular rivalry evaluation before and after 2-hr monocular deprivation (MD) according to the
153 standard protocol (19).

154 On V2, participants were admitted to our Research Unit in the morning after an overnight fast to
155 undergo an oral glucose load (75 g OGTT). Blood samples were obtained at -120, 0, 15, 30, 45, 60, 75,
156 90, 105 and 120 min for determination of plasma substrate and hormone concentrations. All
157 participants underwent RYGB within 2 weeks upon completion of baseline evaluation. Brain plasticity
158 evaluation was then repeated 1 (V3), 3 (V4) and 6 months (V5) after surgical intervention whereas the
159 OGTT was repeated only after 6 months (V6).

160 ***Visual Plasticity Assessment***

161 Experimental procedures took place in a dark, quiet room after an overnight fast. Visual stimuli were
162 generated by a VSG 2/5 stimulus generator (CRS, Cambridge Research Systems) housed in a laptop
163 (Dell, Round Rock, TX, USA) controlled by Matlab programs (MathWorks, Natick, MA, USA). The
164 stimuli consisted in 2 sinusoidal gratings, oriented either 45° clockwise or counterclockwise (size: $2\sigma =$
165 2° , spatial frequency: 2 cpd), presented on a uniform background (luminance: 9cd/m² CIE $x=.311,$
166 $y=.341$) with a central black fixation point and a common squared frame to facilitate dichoptic fusion.
167 Visual stimuli were displayed on a 17-inch CRT monitor (FD Trinitron CRT multiscan G200) monitor,
168 driven at a resolution of 1024x600 pixels, with a refresh rate of 120 Hz. Observers viewed the display
169 at a distance of 57 cm through CRS Ferro-Magnetic shutter goggles that occluded alternately one of the
170 two eyes each frame. Responses were recorded through the computer keyboard.

171 For binocular rivalry assessment, experimental blocks of 125 seconds were used. After an acoustic
172 signal (beep), the binocular rivalry stimuli appeared. Subjects reported their perception (clockwise,

173 counterclockwise or mixed) by continuously pressing with the right hand one of three keys (left, right
174 and down arrows) of the computer keyboard. At each experimental block, the orientation associated to
175 each eye was randomly varied so that neither subject nor the investigators knew which stimulus was
176 associated with which eye until the end of the session. Two binocular rivalry experimental blocks were
177 acquired before monocular deprivation and four blocks after eye-patch removal.

178 Monocular deprivation was performed using an eye-patch of a translucent plastic material that allowed
179 light to reach the retina (luminance attenuation 0.07 logUnits) but completely prevented pattern vision,
180 as assessed by the Fourier transform of a natural world image seen through the eye-patch. The dominant
181 eye (the eye showing longer perceptual predominance in binocular rivalry) was patched for 120-min.
182 During the 2h of monocular occlusion patients were free to perform normal quiet activities (walking,
183 reading, using a computer).

184

185 **Laboratory assays**

186 Plasma glucose concentration was measured using the glucose oxidase method (Beckman, Fullerton,
187 CA, USA). Samples for GIP and GLP-1 were drawn in tube containing protease inhibitors, specifically
188 optimized for stabilization of metabolic markers (BD P800, BD Biosciences, USA). Total GLP-1,
189 active GLP-1 and GIP were measured by ELISA (EDM Millipore, St. Charles, Missouri, USA). Insulin
190 and C-peptide were assessed by radioimmunoassay (IRMA, PANTEC srl Turin, Italy). VIP was
191 measured using an Enzyme Immunoassay (RayBiotech, Norcross, GA, USA). Brain-derived
192 neurotrophic factor (BDNF) and leptin were measured using a Sandwich Enzyme-Linked
193 Immunosorbent Assay (RayBiotech, Norcross, GA, USA).

194 Insulin sensitivity was calculated as ISIcomp according to the formula:

195 $10.000/\sqrt{[fasting\ plasma\ glucose\ (mg/dl) \times fasting\ plasma\ insulin\ (\mu UI/ml) \times glucose\ at\ 120\ min$
196 $(mg/dl) \times insulin\ at\ 120\ min\ (\mu UI/ml)]}$

197 The oral disposition index was calculated as ISSI-2 equal to ISIcomp x AUCins/AUCgluc as previously

198 described (26). The area under the curve of hormones and plasma glucose were computed using the
199 trapezoidal rule.

200

201 *Analyses of visual plasticity*

202 Perceptual reports during binocular rivalry were analyzed using Matlab. We computed the total time (T)
203 during which the observer reported each of the three percepts: the oriented grating presented to either
204 eye (deprived and non-deprived) and a mixture of the two (mixed percepts). To quantify ocular
205 dominance, we defined an index (Ocular Dominance Index, ODI) ranging from 0 (complete dominance
206 of the non-deprived eye) to 1 (complete dominance of the deprived eye), given by:

$$207 \text{ ODI} = T_{\text{DepEye}} / (T_{\text{DepEye}} + T_{\text{NonDep Eye}})$$

208 Eq.1

209 The Ocular Dominance Index does not consider the mixed percepts that do not change after
210 deprivation. The effect of monocular deprivation (Neural Plasticity index, NP) was computed as the
211 difference between the ODI measured after and before the 2h of monocular deprivation.

212

213 *Statistical Analysis*

214 Statistical analyses were performed using SPSS-2.0 (Statistical Package for Social Sciences, Chicago,
215 IL, USA) and Matlab software. Values are presented as mean±SEM or as median (interquartile range)
216 for variables with a skewed distribution; categorical data are expressed as percentages. Variables that
217 were not normally distributed were log-transformed before analysis. Treatment-induced changes were
218 examined by Wilcoxon's signed rank test and a p<0.05 (two-tailed analysis) was considered to be
219 statistically significant.

220 Correlations were assessed by using a robust correlation method (27), the skipped Pearson's correlation
221 coefficient (r) and statistical significance determined by a bootstrap t-test and p-values were corrected
222 for multiple comparisons using the Bonferroni method.

223 To assess the effect of bariatric surgery on visual plasticity, the change in the visual plasticity index
224 (NP) measured before and after surgery was tested with a linear mixed model analysis performed using
225 the fitlme function in Matlab in which time (baseline, 1 month, 3 months and 6 months after surgery)
226 was used as fixed effect with random slope and intercept, with the model: “ $y \sim \text{time} + (1 + \text{time} | \text{ID})$.”
227 Post-hoc tests between the visual plasticity index measured before and after surgery were performed
228 using a Wilcoxon signed rank test, p-values were corrected for multiple comparisons using the
229 Bonferroni method. To determine whether, before surgery, participants with obesity showed a response
230 to monocular deprivation, the plasticity index measured at baseline was compared against the value 0
231 using a Wilcoxon signed rank test.

232

233 **Results**

234 *Participants and Metabolic Parameters*

235 15 subjects with severe obesity completed the neural plasticity assessment, 13 of which also completed
236 the metabolic assessment. Two patients withdrew the consent to repeat post RYGB assessment. The
237 characteristics of the 13 participants who completed the whole study are summarized in Table 1.
238 Participants were relatively young with a baseline BMI of $46.1 \pm 4.9 \text{ Kg/m}^2$. Four subjects had impaired
239 fasting glucose and all the remaining had normal glucose tolerance and HbA1c levels (Table 1). No
240 patient was on any medication known to affect glucose metabolism and brain function.

241 RYGB was followed by a significant reduction in body weight ($-30.5 \pm 0.2 \text{ Kg}$) with a BMI at month 6
242 of $35.3 \pm 5.0 \text{ Kg/m}^2$ ($p=0.001$ vs. baseline). Figure 1 shows the plasma concentrations of glucose, insulin
243 and gut hormones during OGTT. Overall, 6 months after RYGB, plasma glucose and insulin levels
244 showed an earlier peak but lower 2-hour concentration as compared to baseline. Accordingly, ISIcomp
245 (from 2.4 ± 0.5 to 8.2 ± 1.9 ; $p=0.004$) and the Disposition Index (from 1.1 ± 0.2 to 2.9 ± 1.1 ISSI2; $p=0.02$)
246 improved in a significant manner. Total and active GLP1 release in response to glucose ingestion

247 increased after bariatric surgery, while no changes occurred with GIP, VIP, and BDNF. Fasting plasma
248 leptin concentration was significantly lower after RYGB as compared to baseline (Table 1).

249
250 ***Effect of Bariatric Surgery on Visual Cortical Plasticity***
251 Consistently with our previous observations (18), at baseline the neural plasticity index obtained by
252 monocular deprivation was 0.03 ± 0.03 , $p = 0.45$, implying impaired visual cortical plasticity (20).
253 Following RYGB, a progressive increase of the neural plasticity index (Linear Mixed Model Analysis:
254 $t(57)=3.35$, $p=0.0014$) was observed, with ocular dominance shifting in favour of the deprived eye
255 following deprivation, consistently with previous studies on normal-weight subjects (19,20,21). This
256 increase was already statistically significant 3 months after surgery ($p=0.008$) (Figure 2A-B) when an
257 average 25% weight loss was achieved (BMI from 46.1 ± 4.9 to 35.3 ± 5.0 ; $p < 0.01$). Thereafter, the
258 improvement of visual plasticity was constant at 6 months after surgery ($p=0.0036$).

259
260 ***Visual Cortical Plasticity and Glucose Tolerance***
261 Baseline BMI was not correlated with plasticity index (Figure 2C). An inverse correlation was apparent
262 between fasting plasma glucose and the plasticity index ($r = -0.71$; $p=0.02$) (Figure 2D) but not with
263 plasma glucose and insulin concentrations during OGTT before surgery. The plasticity index strongly
264 correlated also with the Disposition Index (and $r=0.75$, $p=0.01$; Figure 2E). No correlation was found
265 between change of BMI, of fasting plasma glucose, of HbA1c and change of plasticity index after
266 surgery.

267
268 ***Brain Plasticity, Gut Peptides, Leptin and BDNF***
269 At baseline plasticity index showed a trend for a negative correlation with total and active GLP1 as well
270 as with GIP, VIP, leptin and BDNF (data not shown). After surgery we found a positive correlation
271 between changes of incremental $AUC_{\text{active GLP-1}}$ and change of plasticity index ($r=0.70$, $p=0.008$; Figure
272 3A). Moreover, six months after surgery leptin was inversely and significantly correlated with

273 plasticity index ($r = -0.63$; $p = 0.02$)(Figure 3B). GIP, VIP and BDNF did not correlate with the plasticity
274 index (data not shown).

275 A multiple linear regression analysis was performed using the change in the different hormones tested
276 as predictors of the change in NP observed 6 months after surgery. The analysis revealed that only the
277 change in active GLP1 was a significant predictor of the plasticity effect ($t = 2.6$, $p = 0.04$), while the
278 other hormones had no significant predictive value (all $p > 0.25$).

279

280 **Discussion**

281

282 This study explored the impact of weight loss obtained by bariatric surgery on brain plasticity and its
283 relationship with circulating gut peptides, leptin, and BDNF. To the best of our knowledge this is the
284 first study exploring visual cortex plasticity (17) during massive weight loss following RYGB and
285 contemporary changes in gut hormones and glucose handling in non-diabetic subjects. The results of
286 our study confirm our earlier finding that morbid obesity is associated with a marked reduction of brain
287 plasticity (18) and reveal for the first time, that this abnormal accommodation of the brain to external
288 stimuli can be progressively reversed by body weight reduction. In fact, the plasticity index improved 1
289 month after surgery to approach values commonly found in healthy subjects after 6 months with a
290 200% increase above the plasticity levels assessed before surgery. The response to monocular
291 deprivation is thought to reflect transient changes in neuronal circuitry in primary visual cortex
292 providing a marker of neural plasticity: changes in visual cortex activity consistent with the deprived
293 eye dominance boost observed at the perceptual level have been observed with different techniques
294 (23,24,28,29). Importantly, it has been shown that the effect of monocular deprivation is also
295 accompanied by a decrease of gamma-aminobutyric acid (GABA) concentration in the primary visual
296 cortex of adult humans (24). GABA is the main inhibitory neurotransmitter in mammalian brain and
297 has been implicated in the control of excitability, information processing, synchronization of neuronal
298 activity and, ultimately, neuroplasticity (30). GABA is also involved in eating behaviour as suggested

299 by experiments in rodents using GABA receptor agonists and antagonists (31). In the animal model,
300 high-fat diet was associated with decreased GABA concentration in the frontal cortex and hippocampus
301 (32). We therefore speculate that changes occurring with body weight reduction can interfere with the
302 GABAergic modulation in the visual cortex and, possibly, in other areas of the brain.

303 The mechanisms responsible for this improvement are not completely clear. However, it is of interest
304 that a number of changes occurring after bariatric surgery showed a relationship with changes in the
305 plasticity index. Thus, plasticity was strongly associated to the metabolic status as indicated by the
306 correlation with plasma glucose and beta-cell function (Disposition Index). Therefore, the worse the
307 metabolic status, the worse the neuronal plasticity although we cannot exclude that similar association
308 may occur with other conditions associated with insulin resistance. In all case, this association is not
309 surprising since it has been shown that insulin signaling can enhance synaptic plasticity by increasing
310 synapsis density in brain regions involved in the processing of visual inputs (33). The well-known
311 peripheral insulin resistance characterizing obesity may well reflect insulin resistance in the central
312 nervous system as previously suggested (34). Therefore, it is tempting to postulate that brain insulin
313 resistance may contribute to impaired activation of synaptic plasticity in the visual cortex of our
314 subjects with obesity. In keeping with this hypothesis, the improvement of insulin sensitivity brought
315 up by body weight reduction was strongly associated with the improvement of the brain plasticity
316 index. These findings also are in keeping with previous studies demonstrating a partial reversibility of
317 impaired insulin-stimulated hypothalamic response (35) after massive reduction of body weight in
318 subjects with obesity (36). The improvement of the plasticity index may be supported not only by
319 amelioration of insulin action but also by changes of other hormones known to exert an effect in the
320 brain. Bariatric surgery is associated with increased GLP-1 response to meal ingestion (37), a finding
321 confirmed in our subjects as well in response to oral glucose load. Much literature supports the central
322 effect of GLP1, so it was not surprising to find an association between changes in GLP-1 levels ensuing
323 RYGB and concomitant changes in the plasticity index. These results can be taken as an additional

324 support to the proposed neuroprotective and synaptic plasticity promoting effects of GLP-1 (38). This
325 relationship is also of interest because of the potential implication of the effect of this hormone in the
326 modulation of satiety and appetite. We have previously shown that the administration of exenatide, a
327 GLP-1 analogue, to subjects with obesity can modify brain responses to food images as monitored by
328 fMRI (14). GLP-1 receptors are expressed in many areas of the human brain (39) where they can
329 participate in high brain functions related to food responses. An effect of GIP is not apparent in our
330 study. Similarly, no association between VIP levels and plasticity index was found. Finally, we have
331 also explored whether signals that are generated by the adipose tissue, the main energy depot in the
332 body, could be linked to changes in brain plasticity that occurred with body weight reduction (i.e. loss
333 of fat mass). To this aim we have measured baseline concentration of leptin, which dropped
334 dramatically after surgery. Leptin is a cytokine and a satiety hormone involved in appetite regulation
335 and energy expenditure modulation. It can cross the blood brain barrier and bind to presynaptic
336 GABAergic neurons to produce its effects and its concentrations are typically increased in human
337 obesity (40). We now report a strong and inverse correlation between reduction in leptin concentration
338 after RYGB and the increase in the plasticity index pointing to another pathway of signal integration
339 between the central nervous system (here probed by the plasticity index) and the energy balance
340 through signals generated in the gut (GLP-1) and adipocytes (leptin). BDNF is widely expressed in the
341 central nervous system, gut and other tissues but was not affected by body weight reduction and showed
342 no association with changes of the plasticity index.

343 The main limitations of our work are the size of the study population and the lack of a control group.
344 However, this was an exploratory study and our results set the basis for future investigation on the
345 relationship between brain plasticity and disturbances of energy metabolism. Similarly, we are totally
346 aware that correlations between metabolic parameters and plasticity index change after surgery do not
347 imply causality, yet they are hypothesis generating and as such our findings can help designing future
348 studies to unravel the complexity of the brain-gut axis.

349 In summary, we have shown that severe impairment of visual brain plasticity occurring in subjects with
350 morbidly obesity can be recovered by reduction in body weight. These improvements may be mediated
351 by amelioration of (brain) insulin sensitivity, increased availability of GLP-1 and strong reduction of
352 leptin resistance, thus supporting the fine integration between the CNS and the periphery.

353

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357 **Competing Interest.** No potential conflicts of interest relevant to this article were reported.

358 **Author Contributions.** GD, MCM, and SDP conceived the objective and designed the study. GD, AD,
359 GC, FS and AC have screened subjects with obesity. GD and AD collected the study data, analyzed the
360 result and wrote the first version of the manuscript. CL, PB and MCM designed, measured and
361 analyzed the visual performance to asses visual plasticity. RB and CM performed RYGB. LG
362 conducted the laboratory analysis. All authors have reviewed and approved the final version of the
363 manuscript. SDP is the guarantor of this work and, as such, had full access to all the data in the study
364 and takes responsibility for the integrity of the data and the accuracy of the data analysis.

365 **Prior Presentation.** Parts of this study were presented at the 79th and 80th Scientific Sessions of
366 American Diabetes Association and the 54th and 55th Annual Meeting of the European Association for
367 the Study of Diabetes

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467 **Figures and Table Legend**

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469 **Figure 1-** Plasma concentrations of gut hormones during OGTT. **A:** Plasma Glucose, **B:** Plasma
470 Insulin, **C:** Total GLP-1, **D:** Active GLP-1, **E:** GIP, **F:** VIP. White circle: before RYGB, Black circle:
471 after RYGB. *:p<0.05.

472 **Figure 2- A:** Effect of monocular deprivation (plasticity index) at baseline and 1, 3 and 6 months after
473 surgery. Error bars represent $1 \pm \text{SEM}$ **B:** Scatter plot reporting the effect of monocular deprivation
474 measured for each participant before and at two different time points after surgery: 1 month (light grey
475 symbols) and 6 months (dark grey symbols). The dashed lines on the 0 value indicate the absence of
476 plasticity (no effect of monocular deprivation). **C:** Correlations before surgery of Neural Plasticity
477 Index and baseline BMI **D:** Correlations before surgery of Neural Plasticity Index and baseline fasting
478 plasma glucose **E:** Correlations before surgery of Neural Plasticity Index Baseline and Disposition
479 Index. All robust correlations are computed by a skipped Pearson correlation (27).

480 **Figure 3- A:** Correlation between 6 months post-pre surgery change in incremental $\text{AUC}_{\text{active GLP-1}}$
481 ($\text{iAUC}_{\text{active GLP-1}}$) and plasticity index. **B:** Correlation between leptin and plasticity index 6 months after
482 surgery. All robust correlations are computed by a skipped Pearson correlation (27).

483 **Table 1-** Anthropometric and metabolic characteristics of study participants at baseline and 6 months
484 after RYGB.

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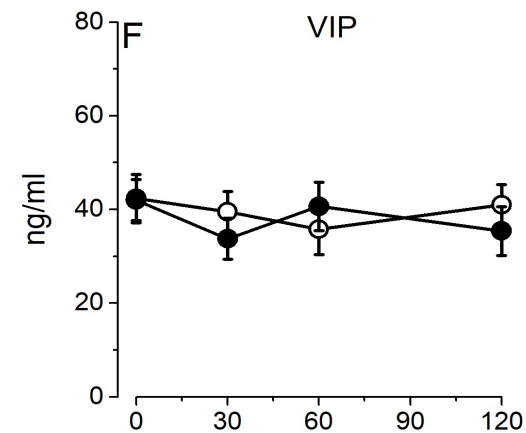
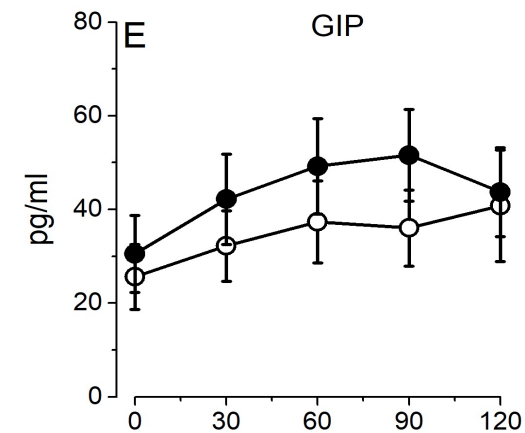
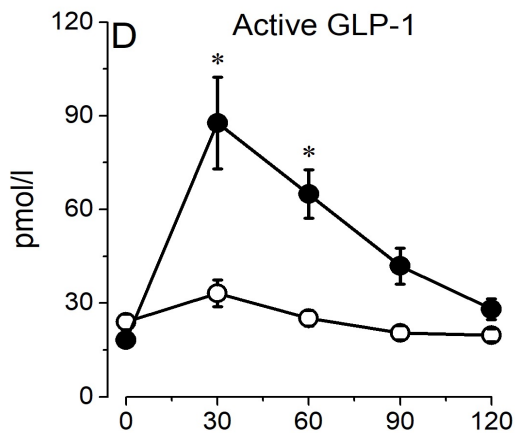
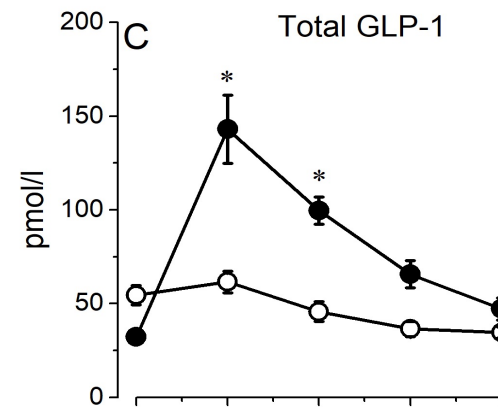
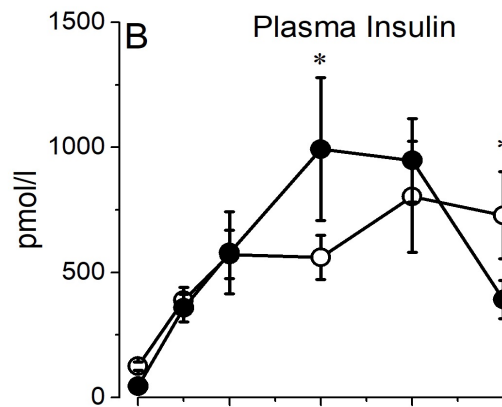
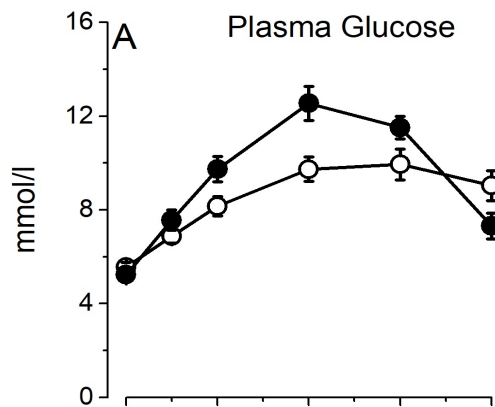
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Characteristic (mean ± SD)	Baseline (n=13)	6-months after RYGB (n=13)	p
Age (years)	42.3 ± 9.8	-	497
Sex (M/F)	2/11		498
BMI (kg/m ²)	46.1±4.9	35.3±5.0	0.001
SBP (mmHg)	129±12	114±5	0.001
DBP (mmHg)	85±9	75±5	0.001
Plasma Glucose (mmol/l)	5.6±0.7	5.2±0.4	ns
HbA1c (mmol/mol)	41±6	38±4	0.01
Total Cholesterol (mg/dl)	192±32	166±21	0.001
HDL Cholesterol (mg/dl)	48±9	54±14	0.02
LDL Cholesterol (mg/dl)	126±31	96±16	0.001
Triglycerides (mg/dl)	111±48	81±29	0.001
Creatinine (mg/dl)	0.7±0.1	0.7±0.1	0.509
AST (UI/l)	20±9	19±5	0.510
ALT (UI/l)	24±19	20±9	0.511
GGT (UI/l)	28±21	14±8	0.01
Matsuda Index (ISIcomp)	2.4±0.5	8.2±1.9	0.004
Disposition Index (ISSI2)	1.1±0.2	2.9±1.1	0.02
Total GLP-1 (pmol/l)	56.6±18.6	32.1±9.9	0.001
Active GLP-1 (pmol/l)	23.9±9.1	18.2±1.1	0.01
GIP (pg/l)	25.6±6.9	30.5±8.1	0.026
VIP (ng/ml)	42.3±17.0	42.0±15.7	0.517
Leptin (ng/dl)	80.4±13.0	16.1±2.4	0.001
BDNF (ng/ml)	196.9±24.5	214.5±52	0.519

520 **Table 1**



Time (min)

