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

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Abstract

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

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

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

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

Introduction

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

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

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

We have recently reported (18) that a particular form of neural plasticity (visual homeostatic plasticity of ocular dominance) is severely blunted in subjects with BMI >40 Kg/m^2. In normal weight adult subjects, a short period of monocular deprivation transiently shifts ocular dominance in favor of the deprived eye both at the perceptual (19,20,21,22) and at the neural level (23,24) reflecting a compensatory regulation of ocular dominance in response to deprivation consistent with homeostatic plasticity (25) We have shown that a strong correlation exists between body mass index (BMI) and this form of visual plasticity (18): the effect of short-term monocular deprivation declines with increasing BMI and is completely absent in subjects with morbidly obesity. Here, we investigate the impact of bariatric surgery on early sensory plasticity and the role of main circulating gut hormones and adipokines in patients with obesity by measuring the effect of short-term monocular deprivation on ocular dominance before and after bariatric surgery.

Subjects and Methods

Participants and Recruitment

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

60 years, BMI >35 kg/m^2, HbA1c <6.5% and eGFR >60 ml/min/1.73m^2 were considered eligible. Individuals with the following conditions were excluded from the study:

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

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

A total of 15 subjects (Age: 42.3 ± 9.8 years, BMI: 46.1±4.9 Kg/m^2) were included in the study. All had normal or corrected to normal visual acuity and no visual deficits. Two participants chose not to complete the oral glucose level test; for these participants, only the neural plasticity results are available.

148

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: 2σ =
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,

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 the investigators knew which stimulus was associated with which eye until the end of the session. Two binocular rivalry experimental blocks were acquired before monocular deprivation and four blocks after eye-patch removal.

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) was patched for 120-min. During the 2h of monocular occlusion patients were free to perform normal quiet activities (walking, reading, using a computer).

Laboratory assays

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

Insulin sensitivity was calculated as ISIcomp according to the formula:

10.000/sqrt [fasting plasma glucose (mg/dl) x fasting plasma insulin (μUI/ml) x glucose at 120 min (mg/dl) x insulin at 120 min (μUI/ml)]

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

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

Analyses of visual plasticity

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

ODI = T_DepEye/(T_DepEye+T_NonDep Eye)

Eq.1

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

Statistical Analysis

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

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

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

Results

Participants and Metabolic Parameters

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

RYGB was followed by a significant reduction in body weight (-30.5±0.2 Kg) with a BMI at month 6 of 35.3±5.0 Kg/m^2 (p=0.001 vs. baseline). Figure 1 shows the plasma concentrations of glucose, insulin and gut hormones during OGTT. Overall, 6 months after RYGB, plasma glucose and insulin levels showed an earlier peak but lower 2-hour concentration as compared to baseline. Accordingly, ISIcomp (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) improved in a significant manner. Total and active GLP1 release in response to glucose ingestion

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

Effect of Bariatric Surgery on Visual Cortical Plasticity

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

Visual Cortical Plasticity and Glucose Tolerance

Baseline BMI was not correlated with plasticity index (Figure 2C). An inverse correlation was apparent between fasting plasma glucose and the plasticity index ($r= -0.71$; $p=0.02$) (Figure 2D) but not with plasma glucose and insulin concentrations during OGTT before surgery. The plasticity index strongly correlated also with the Disposition Index (and $r=0.75$, $p=0.01$; Figure 2E). No correlation was found between change of BMI, of fasting plasma glucose, of HbA1c and change of plasticity index after surgery.

Brain Plasticity, Gut Peptides, Leptin and BDNF

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

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

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

Discussion

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

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

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

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

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

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

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

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

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Figures and Table Legend

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

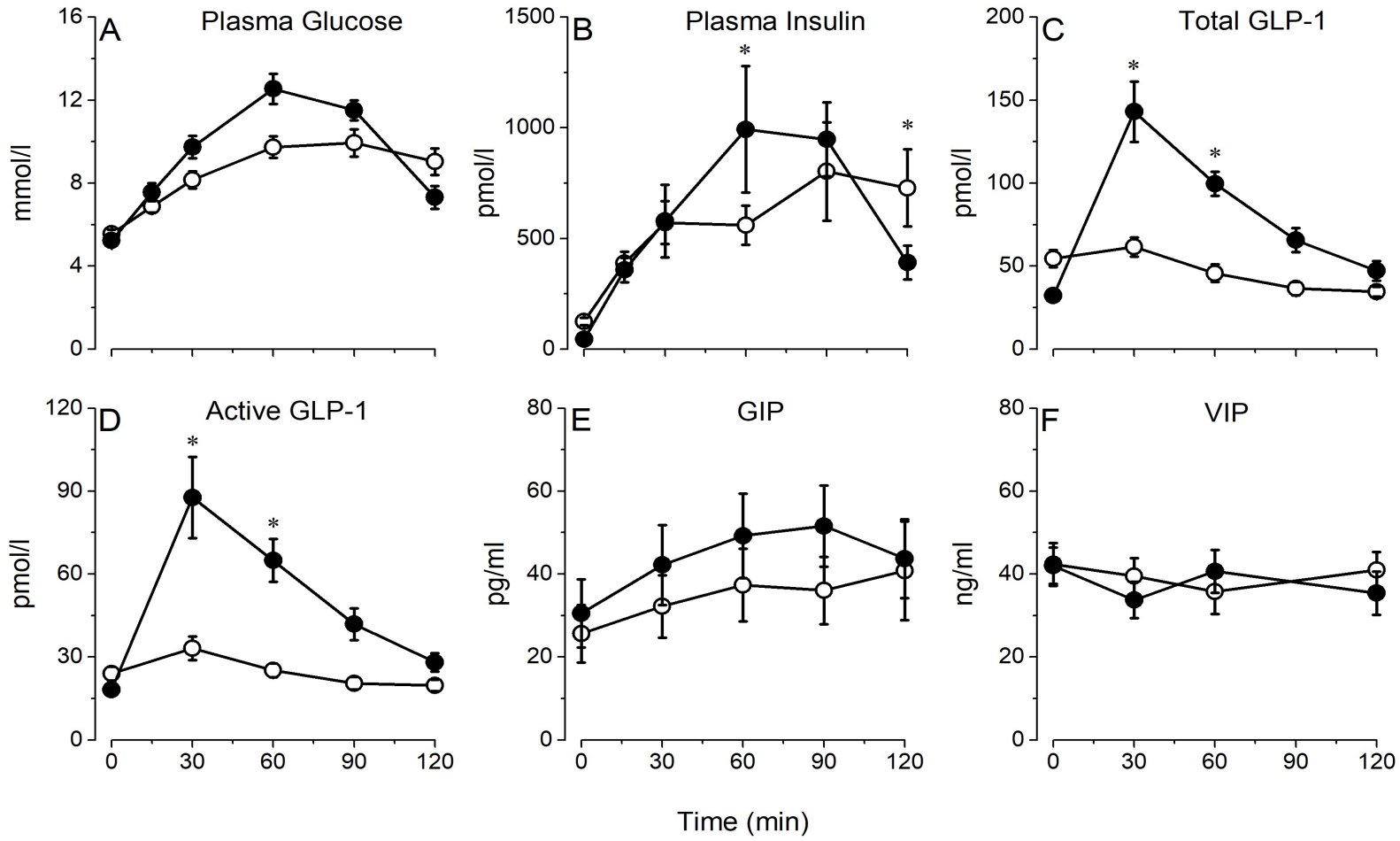
Figure 2- **A:** Effect of monocular deprivation (plasticity index) at baseline and 1, 3 and 6 months after surgery. Error bars represent 1±SEM **B:** Scatter plot reporting the effect of monocular deprivation measured for each participant before and at two different time points after surgery: 1 month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

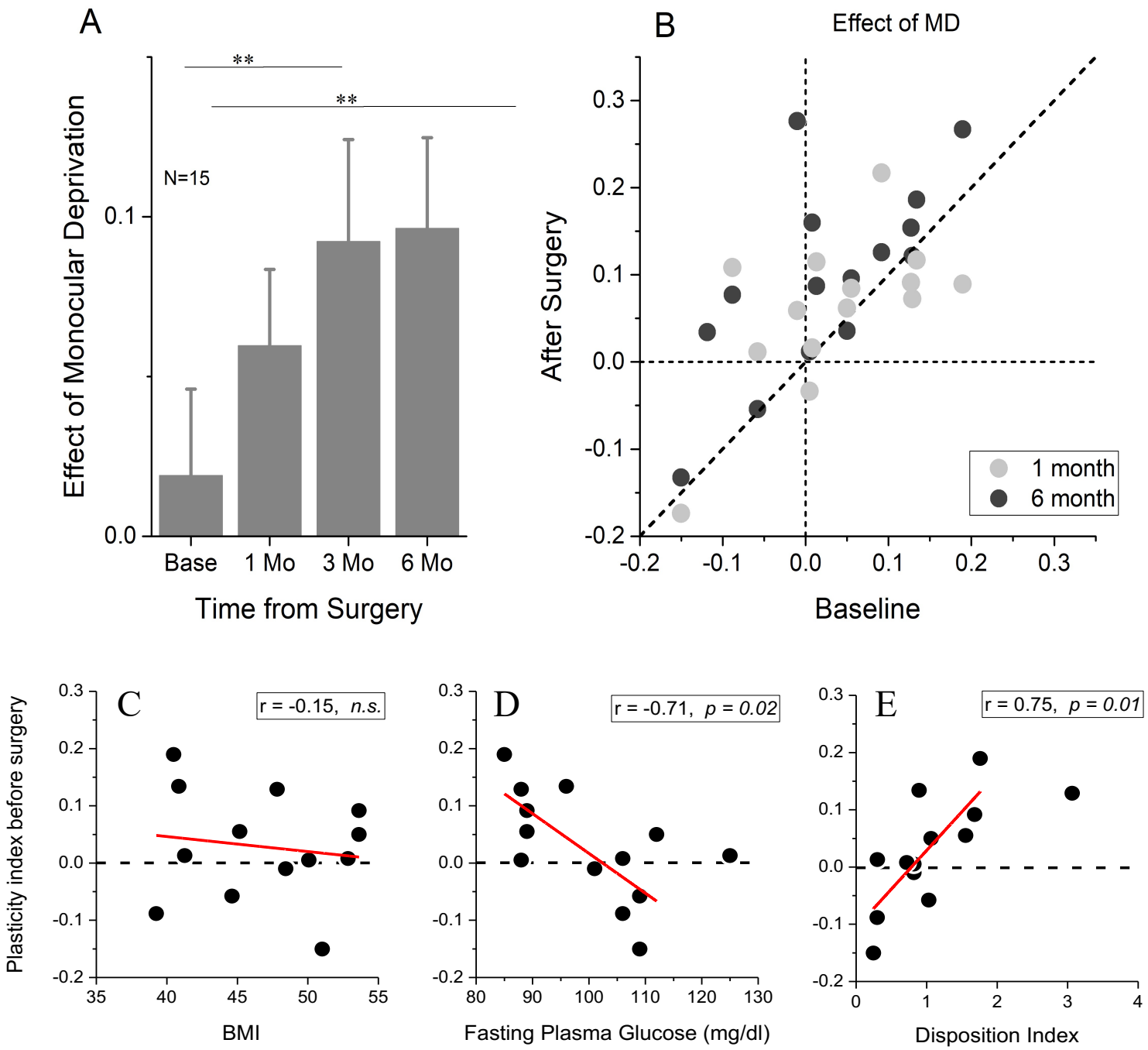
Figure 3- **A:** Correlation between 6 months post-pre surgery change in incremental $AUC_{active\ GLP\text{-}1}$ ($iAUC_{active\ GLP\text{-}1}$) and plasticity index. **B:** Correlation between leptin and plasticity index 6 months after surgery. All robust correlations are computed by a skipped Pearson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

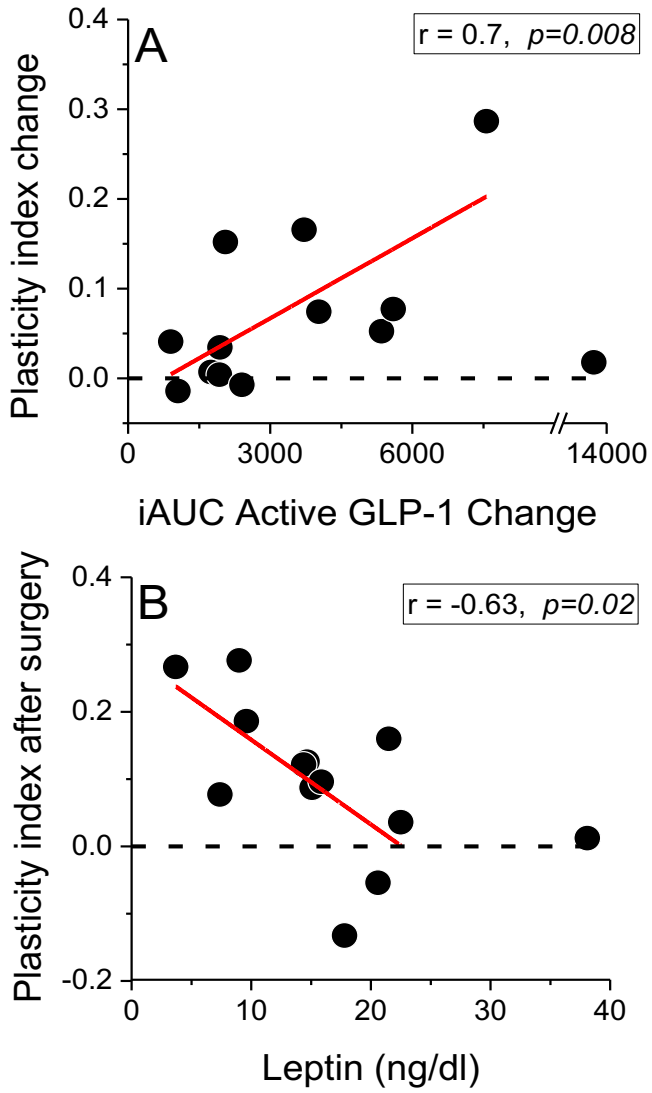
Table 1- Anthropometric and metabolic characteristics of study participants at baseline and 6 months after RYGB.

Characteristic (mean ± SD)	Baseline (n=13)	6-months after RYGB (n=13)	p
Age (years)	42.3 ± 9.8	-	
Sex (M/F)	2/11		
BMI (kg/m^2)	46.1±4.9	35.3±5.0	0.001
SBP (mmHg)	129±12	114±5	ns
DBP (mmHg)	85±9	75±5	ns
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	0.02
Creatinine (mg/dl)	0.7±0.1	0.7±0.1	ns
AST (UI/l)	20±9	19±5	ns
ALT (UI/l)	24±19	20±9	ns
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	0.02
VIP (ng/ml)	42.3±17.0	42.0±15.7	ns
Leptin (ng/dl)	80.4±13.0	16.1±2.4	0.001
BDNF (ng/ml)	196.9±24.5	214.5±52	ns

Table 1


A
Plasma Glucose
mmol/l
16
12
8
4
0
B
Plasma Insulin
pmol/l
1500
1000
500
0
C
Total GLP-1
pmol/l
200
150
100
50
0
D
Active GLP-1
pmol/l
120
90
60
30
0
E
GIP
pg/ml
80
60
40
20
0
F
VIP
ng/ml
80
60
40
20
0
0
30
60
90
120
Time (min)


A
**
**
N=15
Effect of Monocular Deprivation
0.1
0.0
Base
1 Mo
3 Mo
6 Mo
Time from Surgery
B
Effect of MD
After Surgery
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.2
-0.1
0.0
0.1
0.2
0.3
Baseline
1 month
6 month
C
r = -0.15, n.s.
Plasticity index before surgery
35
40
45
50
55
BMI
D
r = -0.71, p = 0.02
80
90
100
110
120
130
Fasting Plasma Glucose (mg/dl)
E
r = 0.75, p = 0.01
0
1
2
3
4
Disposition Index


A
r = 0.7, p=0.008
Plasticity index change
0.4
0.3
0.2
0.1
0.0
0
3000
6000
14000
iAUC Active GLP-1 Change
B
r = -0.63, p=0.02
Plasticity index after surgery
0.4
0.2
0.0
-0.2
0
10
20
30
40
Leptin (ng/dl)