Evaluation and Follow-up of Cognitive Function and Reward Bias in Obesity, and Their Biopsychosocial Determinants: A Prospective Study of Patients with Obesity Before and After Bariatric Surgery

by

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Koç University

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To my husband, Alican Yazıcıoğlu, who has been a constant source of support and motivation and my entire family

ABSTRACT

Evaluation and Follow-up of Cognitive Function and Reward Bias in Obesity, and Their Biopsychosocial Determinants: A Prospective Study of Patients with Obesity Before and After Bariatric Surgery

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Objectives: Obesity, defined by excess accumulation of body fat in the body, is a chronic disease that increases the risk of medical conditions such as hypertension and diabetes, in addition to mental disorders such as depression, and also mortality. People with obesity are at increased risk of dementia and are more likely to have cognitive deficits. It is also argued that individuals with obesity have a reward dependence which makes them vulnerable to addictions other than food. Bariatric surgery (BS) is a preferred treatment for obesity because of its apparent effect on weight loss and recovery from concomitant diseases. It is not well known how BS affects the cognitive function and reward bias in patients with obesity in the early months post-surgery. Here it has been aimed to evaluate and monitor cognitive characteristics and reward responses of patients with obesity at baseline compared to healthy controls and before and after BS, along with determining associated psychiatric symptomatology and stress-related factors using computerized and standard measures, resting-state functional imaging, and potential biomarker measurements. **Methods:** 42 sleeve gastrectomy (SG) patients and 15 healthy controls were evaluated with self-report scales: Snaith-Hamilton Pleasure Scale (SHAPS), Cognitive Failures Scale (CFS), Mood Disorder Questionnaire, Barratt impulsivity, Beck Depression and Beck Anxiety scales to assess psychiatric symptomatology. BS patients were evaluated at baseline, and 3 months post-surgery. Healthy controls were assessed once. Participants completed laboratory-based measures of cognitive function (a neuropsychological test battery, Penn-CNP) and a reward learning task (the probabilistic reward task, PRT). Blood samples were collected at all assessments to assess HOMA-IR, HbA1c, CRP, lipid panel, vitamin B12, folic acid, and ferritin levels. 19 of the BS patients (pre-surgery and 3 months post-surgery) and 15 controls underwent resting-state functional magnetic resonance (fMRI) imaging for evaluation of functional connectivity (FC). The regions of interest on FC were default mode network (DMN), dorsal attention network, medial prefrontal cortex, hippocampus, nucleus accumbens, orbitofrontal cortex (OFC), caudate, putamen, amygdala, insular cortex, and salience network. **Results:** Depression, anxiety, impulsivity, stress, and anhedonia scores, in addition to self-report cognitive symptoms, did not change significantly at 3 months post-surgery compared to pre-surgery in patients with obesity. There was a significant increase in scores related to visuospatial perception and memory (32.53 ± 3.37 vs. 35.21 ± 3.80, $p < 0.001$ for face memory task, 33.97 ± 3.59 vs. 35.92 ± 3.58, $p = 0.001$ for delayed face memory task, 15.26 ± 2.59 vs. 16.13 ± 2.53, $p = 0.002$ for visual object learning task) and visual attention and impulsivity (109.76 ± 12.18 vs. 114.56 ± 6.75, $p = 0.002$ for continuous performance task) between pre-surgery and 3 months post-surgery, along with an increased overall performance score (-0.17 ± 0.81 vs. 0.29 ± 1.07, $p < 0.001$). Mixed-effects

regression analysis revealed that the model was a significant predictor of total correct responses for the visual object learning task (SVT). BMI negatively predicted SVT, while insulin resistance (HOMA-IR), C-reactive protein (CRP) and triglycerides did not. For the other improved cognitive scores, the model including BMI, HOMA-IR, CRP and triglycerides was not significant. There were no statistical differences between patients with obesity and healthy controls regarding Penn-CNP tasks scores at baseline. There was no significant difference in reward bias and discriminability variables, main outputs of the PRT, in the 3 months post-surgery in the group with obesity. When the patient group with obesity was compared with the healthy control group at baseline, patients with obesity had greater response bias (0.144 ± 0.225 vs. 0.072 ± 0.149, $p=0.022$) in PRT. Increased FC was found between the left hippocampus and precuneus cortex post-surgery in patients with obesity. There was a negative correlation between the change in total correct responses in the face memory task (IFAC_TOT) and the right PFC in the salience network in patients with obesity after BS. There were no FC differences in the DMN and in the major areas of the reward network, such as nucleus accumbens, putamen, ventromedial PFC, and the anterior insula post-surgery in the group with obesity. Significant FC changes were observed between patients with obesity and healthy controls. Right anterior insula FC with right supramarginal gyrus (SMG) and right OFC FC with right insular cortex were significantly higher and left amygdala FC with left precuneus was significantly lower in patients with obesity compared to controls. Also, left OFC FC with left frontal pole; left and right putamen FC with left middle and superior frontal gyrus were significantly lower, and right intraparietal sulcus (IPS) with right postcentral gyrus was significantly higher in patients with obesity compared to controls. **Conclusion:** Bariatric surgery may cause improvement of cognitive task scores, even as early as three months post-surgery, however, reward bias in patients may remain unchanged. Our analysis shows that improvement of cognitive function may be devoid of the improvement of HOMA-IR, CRP, and triglyceride levels, but that it may relate to functional connectivity changes in the brain. Other biomarkers as GLP-1, leptin, ghrelin, and inflammatory cytokines might be mediating this relationship and it needs further assessment in conjunction with structural changes in the brain.

ÖZETÇE

Obezitede görülebilen duygusal düzenleme, bilişsel değişiklikler, dürtü kontrol sorunları, ödül sistemindeki bozuklukların bariyatrik- metabolik cerrahi öncesinde ve sonrasında değerlendirilmesi, izlenmesi ve ilişkili biyopsikososyal risk faktörlerinin belirlenmesi

Candan Yasemin Eren- Yazıcıoğlu

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Amaç: Vücutta aşırı yağ birikmesi ile tanımlanan obezite, hipertansiyon ve diyabet gibi tıbbi durumların yanı sıra depresyon gibi ruhsal bozuklukların riskini ve mortaliteyi artıran kronik bir hastalıktır. Obez kişiler, artmış demans riski altındadır ve özellikle yürütücü işlevler ile ilgili gündelik hayatı etkileyebilen bilişsel bozukluklara sahip olma ihtimalleri yüksektir. Ayrıca obez bireylerde bir ödül bağımlılığı olduğu ve bariyatrik cerrahi sonrasında yemek dışındaki maddelere bağımlılık gösterebildikleri savunulmaktadır. Bariyatrik cerrahi, kilo kaybı ve eşlik eden hastalıklardan iyileşme üzerindeki belirgin etkisi nedeniyle obezite için tercih edilen bir tedavidir. Obez hastalarda ameliyat sonrası ilk aylarda bariyatrik cerrahinin bilişsel işlevi ve ödül mekanizmalarını nasıl etkilediği iyi bilinmemektedir. Bu araştırma, obezite ve ilişkili olduğu bilinen psikiyatrik belirti ve bozuklukları sağlıklı kontroller ile karşılaştırarak geniş bir çevçevede incelemeyi, bilişsel belirtiler ve ödül sistemi merkezde olmak üzere obezitenin beyin üzerine olan etkilerinin ortaya konulabilmesini ve bariyatrik cerrahi sonrası bilişsel özellikler ve ödül işleme üzerine olan etkilerini değerlendirmeyi planlamaktadır. **Yöntemler:** 42 tüp mide (TM) ameliyatı hastası ve 15 sağlıklı kontrol psikiyatrik değerlendirme için Snaith-Hamilton Keyif Alma Ölçeği (SHKAÖ), Bilişsel Başarısızlıklar Ölçeği (BBÖ), Duygudurum Bozukluğu Anketi, Barratt Dürtüsellik Ölçeği, Beck Depresyon ve Beck Anksiyete özbildirim ölçekleri ile değerlendirilmiştir. Bariyatrik cerrahi hastaları başlangıçta ve ameliyattan 3 ay sonra değerlendirilmiştir. Sağlıklı kontroller ise yalnızca bir kez değerlendirilmiştir. Katılımcıların bilişsel işlevleri Penn-CNP nöropsikolojik test bataryası ve ödül yanlılığı Probabilistik Ödül Görevi (PRT) ile incelenmiştir. Insulin direnci (HOMA-IR), HbA1c, C-reakif protein (CRP), lipid paneli, vitamin B12, folik asit ve ferritin düzeylerini değerlendirmek için tüm değerlendirmelerde kan örnekleri alınmıştır. Obez hastaların 19'una (ameliyat öncesi ve ameliyattan 3 ay sonra) ve 15 kontrole, fonksiyonel değişikliklerin değerlendirilmesi için dinlenme durumunda fonksiyonel manyetik rezonans (fMRI) görüntüleme uygulanmıştır. Odaklanılan ilgi alanları başlıca medial prefrontal korteks, hipokampus, nükleus akumbens, orbitofrontal korteks (OFC), kaudat, putamen, amigdala, insular korteks, "default mode" (DMN), "dorsal attention" ve "salience" ağlarıdır. **Bulgular:** Depresyon, anksiyete, dürtüsellik, stres ve anhedoni skorları obez hastalarda cerrahi sonrası 3. ayda ameliyat öncesine göre anlamlı bir değişiklik göstermemiştir. Penn-CNP bataryasında, görsel-uzaysal algı ve hafıza ile ilgili görevlerde (32.53 ± 3.37, 35.21 ± 3.80, $p < 0.001$, yüz hafızası görevi için; 33.97 ± 3.59'a karşı 35.92 ± 3.58, $p = 0.001$, gecikmiş yüz hafızası görevi için; 15.26 ± 2.59 'a karşı 16.13 ± 2.53, $p = 0.002$, görsel nesne öğrenme görevi için) ve görsel dikkat ve dürtüsellik ile ilgili görevlerde (109.76 ± 12.18'e karşı 114.56 ± 6.75, $p = 0.002$, sürekli performans görevi için) cerrahi öncesi ve cerrahi sonrası 3 ay arasında

anlamlı bir artış bulunmuştur. Ayrıca, bataryadaki genel performans puanı da (-0.17 ± 0.81 vs. 0.29 ± 1.07, p<0.001) anlamlı bir yükseliş göstermiştir. Çoklu regresyon analizi, vücut kitle indeksinin (VKİ) görsel nesne öğrenme görevinde (SVT) toplam doğru yanıtları negatif olarak etkilediğini göstermiştir. HOMA-IR, CRP ve trigliseritlerin ise SVT üzerinde bir etkisi bulunmamıştır. Penn-CNP puanları açısından obez hastalar ve sağlıklı kontroller arasında istatistiksel fark saptanmamıştır. Obez grupta ameliyat sonrası 3. ayda, PRT'nin ana çıktıları olan ödül yanlılığı ve ayırt edilebilirlik değişkenlerinde anlamlı bir fark tespit edilmemiştir. Öte yandan, obez hasta grubu ve sağlıklı kontrol grubu karşılaştırıldığında, obeze hastalarda PRT'de daha fazla yanıt yanlılığı (0.144 ± 0.225'e karşı 0.072 ± 0.149, p=0.022) bulunmuştur. Obez hastalarda cerrahi sonrası sol hipokampus ve precuneus arasında fonksiyonel bağlantısallık artmıştır. Korelasyon analizi, cerrahi sonrası obez hastalarda yüz belleği görevinde (IFAC_TOT) toplam doğru yanıtlarındaki değişiklik ile "salience" ağındaki sağ ön prefrontal kortex alan arasında negatif bir ilişki saptanmıştır. Cerrahi sonrası, obez hastalarda DMN ve ödül sisteminin ana alanlarında (akumbens, putamen, ön insula) fonksiyonel bağlantı farkı bulunmamıştır. Obez hastalar ve sağlıklı kontroller arasında da önemli fonsiyonel bağlantı değişiklikleri gözlemlenmiştir. Kontrollere kıyasla obez hastalarda sağ supramarjinal girus (SMG) - sağ ön insula ve sağ insular korteks - sağ OFC arasındaki fonksiyonel bağlantı anlamlı olarak yükselmiştir ve sol prekuneus - sol amigdala arasındaki fonksiyonel bağlantı anlamlı olarak düşmüştür. Ayrıca, obez hastalarda kontrollere kıyasla sol ön kutup - sol OFC; sol orta ve üst frontal girus - sol ve sağ putamen arasındaki fonksiyonel bağlantı anlamlı olarak düşmüştür ve sağ postcentral girus - sağ intraparietal sulkus (IPS) arasındaki fonksiyonel bağlantı anlamlı olarak daha yükselmiştir. **Sonuç:** Bariyatrik cerrahi, ameliyattan üç ay sonra bile bilişsel görev puanlarında iyileşme ile ilişkili bulunmuştur, ancak hastalarda ödül yanlılığı değişmemiştir. Analizimiz, bilişsel işlev testlerindeki gelişmenin HOMA-IR, CRP ve trigliserit düzeylerindeki iyileşme ile ilişkisinin olmadığını, ancak beyindeki işlevsel bağlantı değişiklikleriyle ilgili olabileceğini göstermektedir. GLP-1, leptin, ghrelin ve inflamatuar sitokinler gibi diğer belirteçler ve beyindeki yapısal değişiklikler bu ilişkiye aracılık ediyor olabilir; bu konularda daha fazla araştırmaya ihtiyaç vardır.

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ABBREVIATIONS

BMI	Body Mass Index
HFD	High-Fat Diet
SD	Standard Diet
BS	Bariatric Surgery
RYGB	Roux-en-Y Gastric Bypass
SG	Sleeve Gastrectomy
GLP-1	Glucagon-like peptide 1
GLP-1R	Glucagon-like peptide 1 Receptor
AD	Alzheimer's Disease
fMRI	Functional Magnetic Resonance Imaging
SCID-V	Structural Clinical Interview for Psychiatric Disorders-V
BDI	Beck Depression Inventory
BAI	Beck Anxiety Inventory
CTQ	Cognitive Failures Questionnaire
MDQ	Mood Disorder Questionnaire
SHAPS	Snaith-Hamilton Pleasure Scale
BIS	Barratt Impulsivity Scale
CTQ	Childhood Trauma Questionnaire
CSS	Chronic Stress Scale
PSS	Perceived Stress Scale
DT	Distress Thermometer
MSPSS	Multidimensional Scale of Perceived Social Support
PRT	Probabilistic Reward Task
FC	Functional Connectivity
ROI	Region of Interest
DMN	Default Mode Network
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
CRP	C-reactive Protein
PFC	Prefrontal Cortex
VTA	Ventral Tegmental Area
NAc	Nucleus Accumbens

NTS	Nucleus of Solitary Tract
OFC	Orbitofrontal Cortex
RPFC	Rostral Prefrontal Cortex
SMG	Supramarginal Gyrus
FEF	Frontal Eye Field
mPFC	Medial Prefrontal Cortex
IPS	Intraparietal Sulcus
vmPFC	Ventromedial Prefrontal Cortex
dlPFC	Dorsolateral PFC
vSTR	Ventral Striatum
YFAS	Yale Food Addiction Scale

Chapter 1:

INTRODUCTION

1.1 Obesity, brain, and cognitive function

Obesity, defined by excess accumulation of body fat in the body, is a serious and chronic disease that develops due to genetics and environmental factors (Stevens et al., 2012). With its increasing prevalence, obesity has become an important public health issue and has significant clinical and social impacts on societies. The prevalence of severe obesity defined by patients over 40 and 50 body mass index (BMI) has increased by two to three folds, respectively (Sturm, 2007). Recent surveys show that from 1975 to 2014, the global prevalence of obesity changed from 3.2% to 10.8% in men and from 6.4 and 14.9% in women. If this trend continues, it is estimated that 18% of men and 21% of women will become obese worldwide (Abarca-Gómez et al., 2017).

Obesity increases morbidity and mortality, along with the increased risk of medical conditions such as hypertension and diabetes (Ogden, Yanovski, Carroll, & Flegal, 2007), in addition to mental disorders such as depression (Luppino et al., 2010) and dementia. A meta-analysis shows that overweight BMI in midlife is associated with a 1.35 times higher risk of Alzheimer's disease (AD), 1.33 for vascular dementia, and 1.26 increased risk for all causes of dementia compared with normal BMI individuals (Anstey, Cherbuin, Budge, & Young, 2011). This difference still exists even after controlling for demographic variables such as age and sex and medical conditions as hypertension, stroke, heart disease, and diabetes, as patients with obesity are 74 % more likely to develop dementia than normal BMI controls (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005).

Although negative effects of these medical and psychiatric disorders on cognition have been demonstrated clearly, recent studies have shown that obesity has an independent impact on the brain. For example, cognitive impairment for people with high BMI starts even before the onset of their dementia (Hassing et al., 2009; Strazzullo et al., 2010). In a longitudinal study, participants with higher BMI in midlife showed lower cognitive performance in all domains, including long-term memory, short-term memory, speed, verbal, and spatial ability, when assessed 30 years later (Hassing, Dahl, Pedersen, & Johansson, 2010). Research on obese Zucker rats, a widely used model for obesity and type 2 diabetes, shows that obese rats were impaired in spatial memory tasks such as Morris Water Maze (X.-L. Li et al., 2002) and hippocampus-dependent long-term memory tasks such as the Delayed Alternation Task (Winocur et al., 2005). A study on individuals with obesity aged between 18 and 65 shows significant impairments in cognitive functions as worse executive function and processing speed than healthy controls (Prickett, Brennan, & Stolwyk, 2015). Severely participants with obesity also have deficits in learning and recognition memory (Gunstad et al., 2011). In a study on different age groups, individuals with obesity performed worse on memory tasks than normal-weight controls across the adult lifespan (21-82 years old). These results continued to be significant when assessing only younger individuals (21-50 years old). There was no correlation between BMI and age on memory performance, indicating that the relationship between obesity and memory is independent of age (Gunstad et al., 2007). In a recent translational study, middle-aged mice fed with a high-fat diet (HFD) for 12-weeks showed increased locomotor activity at 4-weeks, enhanced depressive-like behaviors at 8-weeks, and memory problems at 12-weeks along with glucose intolerance, hyperglycemia, and weight gain. Changing HFD to a standard diet (SD) for an additional 4-weeks reversed mood and memory impairments and improved metabolic dysfunctions observed (Braga, Delanogare, Machado, Prediger, & Moreira, 2021).

High blood pressure, insulin resistance, gut microbiota alterations, and inflammation in obesity are considered possible mediators in the relationship between obesity and increased risk for dementia (Martins, Monteze, Calarge, Ferreira, & Teixeira, 2019). Some of these cognitive deficits might be related to structural changes in the brain of individuals with obesity, such as a reduced grey matter volume of different parts of the brain such as the prefrontal cortex (PFC), the main center for cognitive functions, and hypothalamus (Rullmann et al., 2018) along with widespread cortical thinning (Veit et al., 2014). Several studies also show that increased BMI correlates with decreased hippocampal volume (Debette et al., 2011) and temporal lobe atrophy (Gustafson, Lissner, Bengtsson, Björkelund, & Skoog, 2004). These brain areas are essential for learning and memory, and changes in these structures might cause an increased risk of AD in individuals with obesity. PET and fMRI research shows an inverse relationship between BMI and brain glucose metabolism, which in turn might affect cognitive functions. Individuals with higher BMI have reduced metabolic activity in the PFC and perform poorly on executive function and memory tasks than healthy controls (Volkow et al., 2009). In other words, obesity has the potential to cause cognitive impairment that may affect daily life before leading to dementia. For this reason, individuals with obesity should be examined carefully in terms of cognitive characteristics, and changes in cognitive functions in the weight loss process should be followed.

1.2 Bariatric surgery and its effect on the brain

Bariatric surgery (BS) is a preferred treatment for obesity because of its apparent effect on weight loss and recovery from concomitant diseases such as diabetes mellitus and hypertension. There are three commonly performed surgery types: Roux-en-Y Gastric Bypass (RYGB), sleeve gastrectomy (SG), and adjustable gastric band. The surgery method is decided based on

patients' BMI, comorbidities, eating habits, and previous surgery history (Khwaja & Bonanomi, 2010) as these methods have differential effects on the outcomes of the surgery. BS usually results in a weight loss ranging between 12-39% of the pre-surgery body weight (Ionut & Bergman, 2011) and increases patients' quality of life (Sockalingam et al., 2017). Despite BS's beneficial outcomes in weight loss, its effect on cognitive function and mood in the longitudinal follow-up are not well studied. Weight loss after BS is associated with cognitive recovery (Spitznagel et al., 2015). RYGB is associated with cognitive improvement, especially memory, 12 weeks and 24 months after surgery (Alosco, Spitznagel, et al., 2014). Spitznagel noted that cognitive improvements are rapid until 24 months post-operative and usually remain at the same level afterward. However, around the time of 36 months post-operation, the patients who started to gain weight showed a decline in some of the cognitive domains (e.g., attention). Specifically, memory, attention, and executive functioning domains of cognition tend to improve drastically after bariatric surgery. Still, patients who suffer from cognitive deficits pre-surgery have poor weight loss outcomes (Marek, Ben‐Porath, & Heinberg, 2016). Several studies are evaluating cognitive functions such as attention and memory before and after bariatric surgery (Veronese et al., 2017). Although rapid weight loss may be associated with a rapid reduction in the brain volume as in anorexia nervosa cases (Titova, Hjorth, Schiöth, & Brooks, 2013), individuals with obesity who underwent bariatric surgery are thought to have an increase in gray matter volumes in the brain as opposed to rapid weight loss (Tuulari et al., 2016). However, this is not shown longitudinally with extensive sample studies. In addition, it is not known which environmental and metabolic factors the predicts recovery in the brain depends on. Only one study shows better white matter structural integrity one month after BS, but this study does not correlate their findings with behavioral tasks and cognitive parameters (Y Zhang et al., 2016).

The most accepted explanation for cognitive improvement after BS is the recovery of other medical conditions such as hypertension, type 2 diabetes, and sleep apnea. Although these medical disorders significantly improve after BS, research fails to directly correlate with improved cognitive function (Alosco, Galioto, et al., 2014). Another factor considered in improved cognition is metabolic function. Studies show that patients with obesity have metabolic dysfunctions and after BS, reduced ALP and insulin resistance are observed, followed by cognitive recovery (Galioto et al., 2015). Neurohormones such as low ghrelin and elevated leptin levels are commonly seen in obesity and are related to both cognitive decline and the development of AD (Al Hazzouri, Haan, Whitmer, Yaffe, & Neuhaus, 2012). Regulation of these hormones after BS is also considered in cognitive recovery (Alosco et al., 2015). In addition, despite its use in type 2 diabetes, currently, glucagon-like peptide 1 (GLP-1)'s repurposing for neuroprotection in multiple neurodegenerative disorders is also discussed. Recent studies show that the use of GLP-1 agonists is neuroprotective, especially in conditions where cognitive impairment is accompanied, and neural degeneration is evident, such as AD and Parkinson's disease (Salcedo, Tweedie, Li, & Greig, 2012). GLP-1 receptor (GLP-1R) overexpression enhances spatial task learning in animal models, and GLP-1R deletion hinders memory formation and synaptic plasticity (Abbas, Faivre, & Hölscher, 2009). A recent study on transgenic mice expressing human amyloid and tau proteins (TAPP) to model AD demonstrates that TAPP mice have learning, and memory impairments compared to wild-type mice. These impairments are worsened when they have insulin deficiency (M. R. King et al., 2020). In animal models, overexpression of GLP-1 receptor (GLP-1R) enhances spatial task learning. Interestingly, GLP-1 agonist treatment reversed these learning impairments and reduced amyloid b and phosphorylated tau expression, indicating a role of GLP-1 on AD independent from its action on diabetes. Based on a systematic review, GLP-1 agonists can have beneficial effects by decreasing apoptosis, increasing cell viability, increasing

neurogenesis, reducing inflammation, and decreasing oxidative stress (Erbil et al., 2019). However, the exact relationship between GLP-1, obesity, and cognition is unclear, and GLP-1's role in cognitive recovery observed after BS needs to be investigated further. Therefore, there might be other influencers such as structural or functional recoveries in the brain altered in individuals with obesity or molecular targets that mediate these processes. Still, a definitive conclusion of the relationship between these functions and cognitions is not achieved.

1.3 Obesity, psychiatric disorders, and bariatric surgery

There is a bidirectional relationship between obesity and psychiatric disorders. Eating disorders, mood disorders, and psychiatric medications are specifically known to induce obesity; on the other hand, obesity may also lead to psychiatric complications such as depression and cognitive dysfunction (KODAMA et al., 1998; Wadden et al., 2007). Depressive symptoms are positively correlated with excess consumption of unhealthy food among college students (El Ansari, Suominen, & Samara, 2015), and mood disorders are linked with increased carbohydrate intake (Corsica & Spring, 2008). The carbohydrate cravings can be that palatable food intake activates the opioid system and results in a pleasure response that temporarily improves mood (Ventura, Santander, Torres, & Contreras, 2014). Almost 66 % of the cases that apply for BS are reported to have a lifetime history of at least one psychiatric disorder, mainly mood, anxiety, and eating disorders (Kalarchian et al., 2007; Lin et al., 2013). Literature also suggests that these patients may present with various symptoms that may affect the outcome of the surgery. Compared to individuals with normal BMI, people with obesity are diagnosed with personality disorders more frequently, and these diagnoses affect the weight loss process of the obese. By increasing impulsivity and neuroticism and decreasing tolerance for frustration, personality disorders may increase calorie intake and increase the use of eating as a coping mechanism (Gerlach, Loeber,

& Herpertz, 2016). After BS, patients have some persisting psychiatric disorders such as depression and body image problems at 24–36-month follow-up, and these comorbidities are negatively correlated with weight loss outcomes (Jumbe, Hamlet, & Meyrick, 2017).

Patients undergoing BS procedures with low depression levels and moderate anxiety symptoms resulted in better surgical outcomes in weight loss (Agüera et al., 2015). Similarly, a negative correlation between pre-surgery depression levels assessed by Beck-Depression Inventory and success at weight loss one year after RYGB surgery is found (Averbukh et al., 2003). Also, general psychopathology scores are negatively correlated with weight loss percentage after laparoscopic SG surgery (Yapici Eser, unpublished data). The effects of BS on psychiatric symptoms are still not apparent. The change in psychiatric symptoms after surgery and the factors determining this change should be monitored during the follow-up of these patients. Although generally BS patients complete a clinical interview for psychiatric symptoms, only half are assessed with a standardized self-report evaluation (Bauchowitz et al., 2005). Therefore, pre-surgery and follow-up psychological assessments are crucial to better understand the process of BS and the determinants of cognitive change during the post-surgery follow-up period.

1.4 Obesity, reward system, and bariatric surgery

In addition to the cognitive problems, some patients with obesity have food addiction problems. Along with the concept of cross-addiction, which refers to the greater potential of an individual with a particular addiction to become addicted to something else, patients with obesity who undergo bariatric surgery and are unable to eat turn to other maladaptive behaviors as coping strategies (Spadola et al., 2017). Patients who have undergone BS may show differences in their personality characters (Bordignon, Aparício, Bertoletti, & Trentini, 2017), and they may have

a tendency for addictions other than food as alcohol and substances (W. C. King et al., 2017). Food addiction may decrease over time (Sevinçer, Konuk, Bozkurt, & Coşkun, 2016), however, alcohol, gambling, shopping, exercise, self-starvation/overeating, and sexual addictions are commonly observed addictive problems faced after BS (Bak, Seibold‐Simpson, & Darling, 2016). A significant number of BS patients reported new-onset or increased substance use after surgery (Kanji, Wong, Akioyamen, Melamed, & Taylor, 2019). In a study, 14 % of gastric bypass surgery patients at least two years post-surgery fulfilled the criteria for substance use disorder (tobacco, sedative, alcohol, cannabis, and cocaine). Interestingly, 70 % of these patients report developing substance use disorder only after the surgery (Reslan, Saules, Greenwald, & Schuh, 2014). In addition, it is thought that these psychological symptoms and addictive behaviors observed before and after surgery may be factors that prevent weight loss and weight maintenance and even result in weight gain after surgery (Montesi et al., 2016). This reward dependency in patients with obesity is even called 'Reward Deficiency Syndrome', and it is believed to have a shared genetic background (Blum et al., 2011).

It has been suggested that in some cases, after BS, there might be changes in the reward processing networks in the brain (Scholtz, Goldstone, & le Roux, 2015). Scholtz argues that success in maintaining weight loss after RYGB is partly caused by the loss of neural reactivity in the brain's reward systems towards food. However, some patients experience adverse outcomes due to this loss of reward from food. Functional imaging research shows different brain activation patterns in response to food pictures in obesity surgery patients compared to unoperated patients with obesity (Scholtz et al., 2014). Research also shows that obesity surgery changes striatal dopamine signaling pathways, a vital component of the reward system when compared with regular dieting (Hankir, Ashrafian, Hesse, Horstmann, & Fenske, 2015). BS is also suggested to normalize the opioidergic system in patients, which is supposed to decrease

reward dependence (H. Karlsson et al., 2016). However, it is strongly hypothesized by many obesity researchers that reduced reward from food after BS might result in cross-addiction problems in which patients turn to other emotion enhancing substances (e.g., alcohol, drugs) to obtain the lost hedonic reward responses. Also, food might be used to minimize negative feelings, and when the reward of food decreases after BS, these patients become more vulnerable to psychological distress, depression, and even suicide (Scholtz et al., 2015). One explanation for addictions after surgery can be that palatable foods and substances/ alcohol activate the same reward circuits in the brain, and when food is restricted, individuals may have a tendency to use another substance that will induce this circuit. Also, both conditions may be related to other neurocognitive abnormalities in domains such as reward learning, decision-making, and executive function (Ivezaj et al., 2017). Another underlying mechanism can be the changes in GLP-1 levels after BS. In obesity, the expected fluctuations in GLP-1 levels in response to palatable food are lost, and excess food intake may result from this insufficient GLP-1 response (Rigamonti et al., 2015). Studies show that RYGB may effectively restore the normal GLP-1 response and contribute to successful weight loss (Jennifer et al., 2017). In addition, GLP-1R's are widely expressed in areas of the mesolimbic reward pathway such as ventral tegmental area (VTA) and nucleus accumbens (NAc), which receive direct projections from the nucleus of solitary tract (NTS) (Alhadeff, Rupprecht, & Hayes, 2012). A recent review conducted by our laboratory demonstrates that GLP-1 not only decreases food intake, but it also decreases cocaine, amphetamine, alcohol, and nicotine use in animal models (Eren-Yazicioglu, Yigit, DOGRUOZ, & Yapici Eser, 2020). Clinical studies on GLP-1 and reward are limited. However, results still indicate a central regulatory role of GLP-1 on the functional connectivity of the reward pathways (Eren-Yazicioglu et al., 2020).

Imaging studies on patients with obesity have also shown a hyperactive brain reward system, including NAc, ventral striatum, amygdala, orbitofrontal cortex (OFC), and anterior insula (Kenny, 2011). Along with this hyperactivity, disrupted network connectivity within these areas is also reported, further contributing to hyperphagia and obesity (Ivezaj et al., 2017). Studies have been limited in determining whether addiction observed in these people is in search of a continuous substance as a cognitive feature or whether it is difficult to terminate it as an impulsive behavior when encountered with a pleasurable substance, even though there are no reward-seeking reward dependence abnormalities. The tendencies of these people to different addictive substances may depend on their lifestyles and impulsive personalities, or they may always be in search of rewards by showing higher reward sensitivities. Continuing reward bias after surgery may lead to a re-gain of weight in the follow-up of patients. Also, it may cause dependence on other substances, which may lead to decreased quality of life. For this reason, there is a need to evaluate the reward responses in this group longitudinally with a more standardized method that is independent of pleasurable stimuli.

1.5 Aims & Hypothesis

Aim 1: To evaluate and monitor cognitive characteristics before and after sleeve gastrectomy in patients with obesity. Cognitive function is an essential component of psychiatric disorders. People with obesity are at increased risk of dementia and are more likely to have cognitive deficits, especially executive function problems, affecting everyday life. For this reason, individuals with obesity were examined and monitored in more detail in terms of their cognitive characteristics and the change of cognitive functions during the weight loss process after SG. Cognitive changes caused by obesity, which is considered a metabolic disease model affecting the brain, were assessed and followed up in a multidimensional manner after surgery with computerized and standard cognitive measurement methods.

Hypothesis 1: We expect pre-surgery individuals with obesity to have cognitive deficits, especially in executive functioning. Other domains of cognition that rely on executive function and the prefrontal cortex, such as working memory, visual-spatial learning, and memory, attention, problem-solving, are also expected to be impaired. Correlating with weight loss, we expect to see cognitive improvement at 3-months after SG. These results will depend on the success of surgery evaluated by weight loss.

Aim 2: To examine the relationship between obesity, sleeve gastrectomy, and reward processing system. It is argued that individuals with obesity have a reward dependence and that they may be addicted to substances other than food after SG. Studies have been limited in determining whether addiction in these people is due to a search for a continuous substance as a cognitive feature or whether it is difficult to terminate it as an impulsive behavior when encountered with a pleasurable substance, even though there is no reward-seeking or reward dependence. Reward responses were assessed throughout the course after SG with standardized measures, which are independent of pleasurable stimuli.

Hypothesis 2: We expect pre-surgery individuals with obesity to have a high response bias favoring the rich stimulus compared to controls. After SG, these patients' response bias is still expected to be similar to that of pre-surgery results. PRT is a measure of anhedonia, which needs a longer time period to show significant reward changes compared to phasic reward responses such as measurement of cocaine abuse.

Aim 3: Determination of the neuroanatomical and molecular components of cognitive and reward system changes observed after sleeve gastrectomy. In addition to cognitive and reward response assessments, resting-state MRI before and after obesity surgery was taken to better understand accompanying changes in the brain as a result of cognitive impairment. Also,

during the dynamic process following SG, various metabolites and chemokines changes related to glycemic control and inflammation may affect brain health and cognition. Therefore, metabolic alterations such as glucose metabolism parameters, lipid panel, and CRP levels were also assessed.

Hypothesis 3: We expect hyperactive connectivity within the regions of the reward circuit such as NAc, amygdala, OFC, and anterior insula before surgery, along with high reward sensitivities. However, similar to the assumptions on PRT, we expect to see no significant change in the connections between reward processing regions such as the NAc and VTA, along with the OFC, which is essential for reward-driven decision making between pre-and post-surgery results. On the other hand, the PFC and default mode network (DMN) connections are expected to correlate with improved cognitive function after BS.

Chapter 2:

MATERIALS AND METHODS

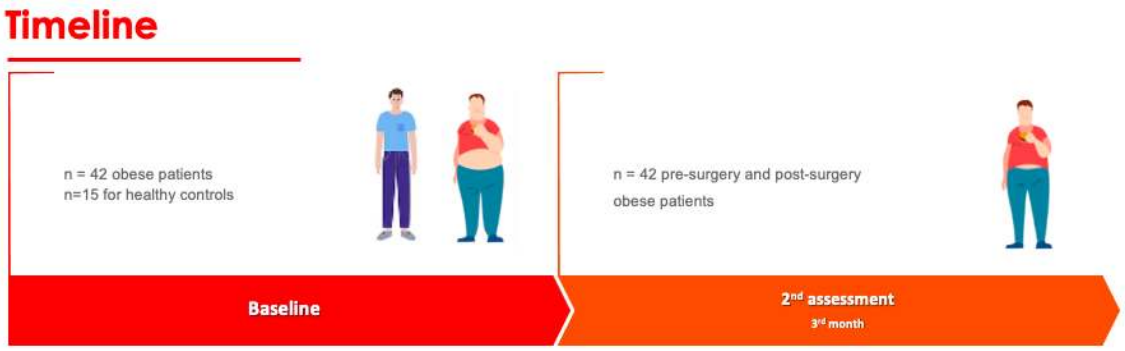
2.1 Participants

Patients who were diagnosed with obesity (body mass index (BMI) ≥ 40 kg/m^2 or > 30 kg/m^2 with concurrent medical complications such as type 2 diabetes mellitus, arterial hypertension, dyslipidemia, obstructive sleep apnea) and have applied to the Koç University Hospital, Department of Psychiatry for evaluation before laparoscopic sleeve gastrectomy (SG) and are approved for surgery were invited to the study. The study included two groups; the first group was composed of patients with obesity undergoing SG, and the second group was composed of healthy volunteers. Healthy controls are compared with pre-surgery patients with obesity to identify possible obesity-related differences at baseline. A total of 42 patients with obesity were recruited for evaluation with clinical scales, and 19 of them were taken to the resting-state functional magnetic resonance (fMRI) imaging step. For the healthy control group, 15 participants were recruited.

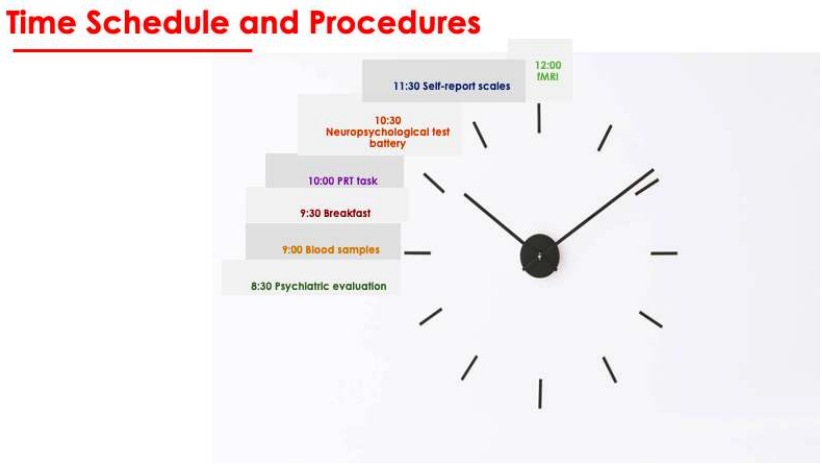
The inclusion criteria for the patients with obesity were being diagnosed with obesity (BMI > 30), being between ages 18-65 years old, being a candidate for SG, and fluency in reading and writing in Turkish. The exclusion criteria of the study were having a disturbance to speech, a history of cancer, dementia, neurological disease, mental retardation and marked cognitive impairment, psychoactive substance use disorder diagnosis, which may have a high impact on the general medical condition and being medically unstable. Healthy controls were in the normal range for BMI; all other criteria were the same. All procedures in the study were in

accordance with the Declaration of Helsinki. This study has been approved by Koç University Institutional Review Board (2017. 081. IRB1. 011).

All batteries were administered for 2 hours in total. Blood samples were collected when they first arrived in a fasted state; afterward, they had a standard breakfast before starting the computer-based tasks. All evaluations were repeated at baseline and 3 months post-surgery. Scores obtained for each test were monitored regarding changes between pre- and post-operation (Figure 2.1).



(a)



(b)

Figure 2.1 Timeline of the study showing assessment time points and study design. (a) This study included a baseline visit before surgery and a follow-up visit at 3 months post-surgery in SG patients with obesity. Healthy controls were only assessed once at baseline. (b) Each visit included a psychiatric evaluation, blood sample collection, a reward-learning task, a neuropsychological test battery, completion of self-report scales, and a resting-state functional imaging session.

2.2 Evaluation of Cognitive and Other Psychiatric Symptoms

Patients were asked to complete a neuropsychological test battery that lasted approximately 90-110 minutes based on performance over the computer system. In the battery, depressive and anxious symptomatology, anhedonia and reward learning, impulsivity, cognitive function, and stress factors such as perceived stress, chronic stress, childhood trauma, and perceived social support were assessed. Lifetime psychiatric history was obtained in the sociodemographic data form in addition to the structured clinical interview. The battery was administered before and 3 months after SG for the patient group with obesity and once for the healthy volunteers.

2.2.1 **Evaluation for Psychiatric Diagnosis***:*

Structured Clinical Interview for Psychiatric Disorders- V (SCID-V): The first psychosocial evaluation of the patients was performed by a structured clinical interview (SCID-V) by a psychiatrist. SCID-V is a structured interview, which takes approximately 30 minutes to identify psychiatric disorders based on DSM-V classification and diagnostic criteria.

2.2.2 **Evaluation of Psychiatric Symptomatology***:*

Beck Depression Inventory (BDI) is a self-report measure of depression levels developed by Beck et al. (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The scale contains 21 items with a 4-point scale. The total scores are calculated by adding up scores of individual items with a maximum score of 63, and higher scores indicate greater levels of depression. The total scores range between 0 to 63: minimal depression (0-9), mild depression (10-18), moderate depression (19-29), and severe depression levels (30-63). Turkish validity and reliability of the scale were performed by Hisli et al. (Hisli, 1989).

Beck Anxiety Inventory (BAI) is a self-report measure of anxiety developed by Beck et al. (Beck, Epstein, Brown, & Steer, 1988). The scale contains 21 items with a 4-point scale. The total score is measured by a summary of individual items. The total scores range between 0 to 63: minimal anxiety (0-7), mild anxiety (8-15), moderate anxiety (16-25), and severe anxiety levels (26-63). Turkish validity and reliability of the scale were performed by Ulusoy et al. (Ulusoy, Sahin, & Erkmen, 1998).

Cognitive Failures Questionnaire (CFQ) is a self-report developed by Broadbent et al. (Broadbent, Cooper, FitzGerald, & Parkes, 1982) which evaluates the possibility of encountering failures in everyday tasks. The scale contains 25 questions assessed with a 4-point scale. Total scores are obtained by adding up the scores of the individual items, which gives a result between 0-75. The total score implies the frequency of cognitive failures experienced. Validity and reliability of the 4-point Likert Turkish version of the scale were performed by Yapici-Eser et al. (H. Y. Eser, Inan, et al., 2020).

Mood Disorder Questionnaire is a 15 items self-report questionnaire developed by Hirschfield et al. (Hirschfeld et al., 2000) to screen for a lifetime history of manic or hypomanic symptoms. The first 13 items are “Yes” or “No” questions derived from DSM-IV and clinical experience; the 14th item assesses whether the manic or hypomanic symptoms are experienced within the same period, and the last item questions the level of dysfunction due to these symptoms. The scale is originally developed for screening of bipolar spectrum disorder. The validity and reliability of the Turkish version were performed by Konuk et al. (Konuk et al., 2007).

Snaith-Hamilton Pleasure Scale (SHAPS) was developed by Snaith et al. (Snaith et al., 1995) to measure anhedonia and hedonic capacity. It contains 14 items based on "Agree" and "Disagree" answers. The total scores are calculated by adding up the scores of individual items with a maximum score of 14. A cut-off score of 2 discriminates between anhedonia and the normal state of anhedonia, and greater scores indicate higher anhedonia levels. Turkish validity and reliability of the scale were performed by Yapici-Eser et al. (H. Y. ESER, İNAN, et al., 2020).

Barratt Impulsivity Scale (BIS) is a self-report scale developed by Patton et al. (Patton, Stanford, & Barratt, 1995) used to assess impulsivity. The scale contains 30 items using 4-point ratings; the total scores are obtained by adding individual items. It also contains subscales such as attentional, motor, and non-planning impulsivity. The validity and reliability of the Turkish version were conducted by Gulec et al. (Güleç et al., 2008).

2.2.3 Evaluation of Stress Exposure and Perception:

Childhood Trauma Questionnaire (CTQ) is a 28-item self-report questionnaire to assess an individual's understanding of childhood trauma experiences. The scale originally contains 70 items developed by Bernstein (Bernstein et al., 2003). In this task, a shorter version with 28 questions assessed with a 7-point scale is used. Total scores are obtained by adding up the individual items (the scale contains reverse items), resulting in between 25-125. Turkish version was developed by Şar et al. (Sar, Ozturk, & Ikikardes, 2012).

Chronic Stress Scale (CSS) is a self-report questionnaire developed by Turner RJ et al. (Turner, Wheaton, & Lloyd, 1995), aimed at assessing ongoing and persistent sources of stress and the

perception of stress in an individual's life. The questions are about stressful life conditions and situations such as financial issues, work, relationships, social life, etc. The scale contains 51 questions assessed using a scale of 3-point (0-2). Total scores are obtained by adding up the individual items, which results in between 0-102, and higher scores indicate higher levels of chronic stress.

Perceived Stress Scale (PSS) is a self-report scale to measure an individual's perception and appraisal of stressful situations. It asks about feelings and thoughts about stressful events during the last month. It was developed by Cohen (Cohen, Kamarck, & Mermelstein, 1994) and contained 14 questions assessed with a 5-point scale. Total scores are obtained by adding up the individual items (the scale has reverse items), which results in between 0-56, and higher scores represent higher perceived stress. The Turkish version of the scale was done by Eskin et al. (Eskin, Harlak, Demirkiran, & Dereboy, 2013).

Distress Thermometer (DT) is a single-item questionnaire to assess psychological distress. It is a 10-point scale; 0 indicates the minimal level of distress, and 10 indicates the maximal distress level. It is originally developed to screen psychological distress in cancer patients (O'Donnell, D'Alton, O'Malley, Gill, & Canny, 2013). A cut-off score of 3 indicates elevated levels of distress. Validity and reliability of the Turkish version of the scale were conducted by Ozalp et al. (Özalp, Cankurtaran, Soygür, Özdemir Geyik, & Jacobsen, 2007).

Multidimensional Scale of Perceived Social Support is a 12 item self-report scale developed by Zimet et al. (Zimet, Dahlem, Zimet, & Farley, 1988) to assess social support. Three subscales are derived for different sources of social support: family, friend, and significant other. Total scores are calculated by adding up the individual items and dividing them by 12. A mean total

score of 1 to 2.9 is considered low support; a score between 3 to 5 is considered moderate support, and a score from 5.1 to 7 is considered high support. The Turkish version of the scale was performed by Eker et al. (Eker, Arkar, & YALDIZ, 2001).

Patients filled these scales using the Qualtrics program on tablet or desktop computers. Evaluations other than CTQ were re-administered from these scales at the 3rd month after sleeve gastrectomy (SG).

2.2.4 Evaluation of Objective Cognitive Function

The cognitive functions of the patients were assessed, pre- and post-operationally (3rd month), by the Penn-CNP neuropsychological test battery and the 'Cognitive Failures Questionnaire' indicated above.

For the evaluation of objective cognitive function, the Turkish version of Penn-CNP has been used (Izgi et al., 2021). Penn CNP is a neuropsychological test battery developed by Prof. Dr. Rachel Gur at the University of Pennsylvania and already in use on large sampled and multi-centered research. This battery is translated into Turkish by establishing a connection between Dr. Hale Yapici Eser and these research centers. Penn-CNP is currently being used in most study conducted by Dr. Hale Yapici Eser and our research team. Below is a list of the tasks selected within the battery.

Continuous Performance Task (PCPT-NL) in the PENN-CNP neuropsychological battery is used to assess visual attention function and impulsivity. In this task, a series of red vertical and horizontal lines flash in a digital numeric frame. Participants should press the space key when

these lines form exact numbers or letters. The task is divided into two parts: the participants first look for complete numbers for 3 minutes and then for complete letters for another 3 minutes.

Conditional Exclusion Test (PCET) in the PENN-CNP neuropsychological battery is used to assess abstraction in the executive function. Participants should choose what object out of four they think is not related to the other three. There are three criteria (line thickness, shape, and size) to select the correct object; the applied criterion changes when the participant has ten consecutive correct answers for each principle.

Face Memory (CPF) *and* ***Delayed Face Memory (CPFD) Tasks*** are used to assess facial memory. Participants see 20 faces that they are being asked to identify later during immediate and delayed recalls. In the immediate recall (CPF), they see 40 faces (20 previously seen and 20 novel faces) and are asked to identify previously seen ones. In the delayed recall (CPFD), the procedure is the same as the immediate recall but takes place 15-45 minutes after the initial session, with other tasks in between to control delay time and avoid rehearsal. Scoring for both tasks is based on the number and median response times of true/false positive/negative responses.

Letter and Back (LNB2) Task is used to assess working memory. Letter-and-Back asks participants to focus on letters on the screen and press the spacebar according to specific rules. The task consists of three parts: 0-back, 1-back, 2-back. During 0-back, participants press the spacebar when they see the letter "X" on the screen. During 1-back, participants press the spacebar when they see the same letter twice. During 2-back, participants press the spacebar when the letter on the screen is the same as the letter before the previous letter. The scoring

consists of the total number of true and false positives and the correct responses' reaction times. Sub-scorings are also performed for all three parts of the task.

Visual Object Learning (SVOLT) *and* ***Visual Object Learning Memory (SVOLTD) Test*** assess visuospatial perception and memory. Participants see ten three-dimensional Euclidean shapes during the visual object learning task (SVOLT). Later, they see 20 shapes and are asked to identify previously seen ones. In the delayed version, the same assessment part is repeated 15-30 minutes after the initial viewing, with other tasks in between to control delay time and avoid rehearsal. Scoring for both tasks is based on the number and median response times of true/false positive/negative responses.

For each test applied with this battery, the test results are automatically calculated by the system, and the response time, correct and incorrect answers for each response are also presented in an analytical data format. All the test scores used for our analysis are listed in Table 2.1. The program also does unbiased arithmetic calculations on important data for further analysis.

Table 2.1 Penn-CNP Variables List

CPF_TP	True Positives for Face Memory Test (CPF)
CPF_TN	True Negatives for CPF
CPF_FP	False Positives for CPF
CPF_FN	False Negatives for CPF
IFAC_TOT	Total Correct Responses for CPF
CPFD_TP	True Positives for Delayed Face Memory Test (CPFd)
CPFD_TN	True Negatives for CPFd

CPFD_FP	False Positives for CPFd
CPFD_FN	False Negatives for CPFd
DFAC_TOT	Total Correct Responses for CPFd
LNB_TP	True Positive Responses for Letter-N-Back (LNB)
LNB_FP	False Positive Responses for LNB
LNB_TP2	True Positive Responses for 2-Back Trials
LNB_FP2	False Positive Responses for 2-Back Trials
CPN_TP	True Positive Responses for Number Trials
CPN_FP	False Positive Responses for Number Trials
CPN_TN	True Negative Responses for Number Trials
CPN_FN	False Negative Responses for Number Trials
CPL_TP	True Positive Responses for Letter Trials
CPL_FP	False Positive Responses for Letter Trials
CPL_TN	True Negative Responses for Letter Trials
CPL_FN	False Negative Responses for Letter Trials
CPT_TP	Total True Positive Responses for Continuous Performance Test (CPT)
CPT_FP	Total False Positive Responses for CPT
CPT_TN	Total True Negative Responses for CPT
CPT_FN	Total False Negative Responses for CPT
PCET_CR	Number Correct Responses for Penn Conditional Exclusion Task (PCET)
PCET_ER	Number Incorrect Responses for PCET
PCET_PER_ER	Number of Perseverative Errors for PCET
PCET_PER_RES	Perseverative Errors Plus Correct Perseverative Responses for PCET

SVT	Total Correct Response for Short Visual Object Learning Test (sVOLT)
SVT_TP	True Positives for sVOLT
SVT_TN	True Negatives for sVOLT
SVT_FP	False Positives for sVOLT
SVT_FN	False Negatives for sVOLT
SVT_LD	Total Correct Response for Delayed Short Visual Object Learning Test (sVOLTd)
SVTLD_TP	True Positives for sVOLTd
SVTLD_TN	True Negatives for sVOLTd
SVTLD_FP	False Positives for sVOLTd
SVTLD_FN	False Negatives for sVOLTd

In addition to analyzing individual test scores, a general factor, "g" is calculated as an overall performance score. The "g" factor comes from a bifactor model (T. M. Reise, 2010) and is calculated by taking the mean of the Z scores of accuracy results from the CNP tests (Moore, 2014). The values taken as accuracy for each test are listed below (Table 2.2).

Table 2.2 Penn-CNP accuracy values for "G" factor analysis

IFAC_TOT	Total Correct Response for Face Memory Test (CPF)
DFAC_TOT	Total Correct Response for Delayed Face Memory Test (CPFd)
LNB_TP	True Positive Responses for Letter-N-Back (LNB)
CPT_TP	Total True Positive Responses for Continuous Performance Test (CPT)

PCET_ACC2	Accuracy for Penn Conditional Exclusion Task (PCET)
SVT	Total Correct Response for Short Visual Object Learning Test (sVOLT)
SVT_LD	Total Correct Response for Delayed Short Visual Object Learning Test (sVOLTd)

For quality control, scores from tasks were standardized across individuals (Z scores) for each session, and the distribution of the Z scores within each participant was assessed. Scores greater than 3.5 standard deviations below or above the mean were considered outliers for all responses and were removed from the data. Out of 42, 3 participants were excluded from the whole task (1 person did not complete the battery and 2 people failed to understand the tasks), and 4 participants were excluded from certain parts after quality control.

2.3 Objective Assessment of Reward Response

The reward response bias of the patients and controls was assessed with the "Probabilistic Reward Task (PRT)" pre and 3rd after SG to examine the changes in the reward learning after surgery.

PRT is a signal detection task used for measuring hedonic capacity and reward learning based on monetary reward enhancement. Developed by Diego Pizzagalli in 2005 (Pizzagalli, Jahn, & O'Shea, 2005), PRT is an objective assessment of the participants' tendency to modulate their behavior in relation to the prize. Subjects are asked to choose between two very similar stimuli at each trial. The stimuli consist of simple cartoon faces (diameter 25 mm, eyes 7 mm) presented at the center of the monitor. There is no mouth at the beginning of the experiment, and after a

certain delay, a 10 mm ("short mouth") or 11 mm ("long mouth") straight mouth is presented for 100 ms (Figure 2.3). Subjects are instructed to press the appropriate button to determine whether the stimulus is presented with a long or short mouth. In a single session, there will be 3 blocks of 100 trials. 40 correct trials are immediately presented with reward feedback in each block: "True! You have earned 0.25 Turkish Lira (TL)". One of the stimuli, the "rich stimulus" (30/40), is awarded three times more often than the other, "lean" (10/40), but the participants do not know about it. The reward feedback is applied with a pseudo-random sequence, and there is randomization in “rich” and “lean” stimulus between participants. If participants respond incorrectly, the reward is delayed until the correct response for the same stimulus type.

This reinforcement method leads to response bias in healthy controls, and more frequent rewarding stimuli are preferred. The response bias towards the more frequently rewarded stimuli will be used to operationalize reward sensitivity. This operationalization is based on previously established ideas on reinforcers playing an important role in associations between salient cues and the internal reward systems (Pizzagalli et al., 2005). Pizzagalli previously reported that depressed individuals show significantly decreased response bias compared to controls (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). Test analysis will have two important data outputs: discriminability (to understand the difference between the two lips) and response bias. Both outputs are given as both total (for the complete task) and main (only including 2nd and 3rd block). While response bias measures the reward responses, discriminability output will indicate executive function. Due to participation and validity of the test, participants will be given 20 TL independently from their performance. The long lip and short mouth pictures used in the program are presented below as an example.

Figure 2.2 Two target stimuli of PRT: "long" and "short" mouth, respectively.

For all analyses in the PRT task, calculations of "response bias" and "discriminability" were made for each block separately, and the overall performance. Based on previous literature on PRT (Pizzagalli, 2008), trials with RT shorter than 150 ms and longer than 2500 ms were excluded, and after natural log transformation, outlier trials were also excluded (mean ± 3SD).

2.4 Neuroanatomical and Molecular Components

2.4.1 Imaging Studies

Structural and functional changes in the brain were evaluated by 3-Tesla Siemens Magnetom Skyra syngo magnetic resonance (MR) machine and 64-channel head coil. Functional magnetic resonance images for evaluation of functional changes were obtained. Specified parameters were used for imaging: T1-weighted Mprage sequence parameters applied were as follows; (TR)/ (TE): 1900 / 2.52 ms, flip angle= 9°, field of view (FOV) = 250 mm, 192 slices, voxel volume= 1 × 1 × 1 mm. Patients were asked to rest their eyes closed for 6 minutes without having any specific thoughts to obtain gradient T2-weighted echo-planar images (EPIs) for resting fMRI. BOLD-weighted functional T2-weighted echo-planar imaging was conducted in an inclined plane parallel to the anterior commissure and posterior commissure; TR= 3000 ms, TE=30 ms, flip angle = 85°, image area=216 mm, 47 slices (for the whole brain), slice thickness=3 mm. MRI examinations were repeated for the patient with obesity group before surgery (0 months) and after 3 months. Healthy controls were only assessed once. Total imaging time was approximately 30 minutes.

Resting-state fMRI analysis: Functional images were analyzed with the CONN functional connectivity toolbox for SPM based on MATLAB 2021b.

In pre-processing, the default pipeline of CONN was used, including functional realignment and unwarping, slice-timing correction, functional and structural normalization, structural segmentation, outlier detection, and functional smoothing (smoothing kernel:6 FWHM). Denoising was performed with covariates (white-matter and cerebrospinal fluid signals) and band-pass filtering with the default CONN values (0.008–0.09 Hz). A component-based noise reduction (Com-pCor) is used to identify and remove the effects of physiological non-neural noise sources, residual subject-related motions, and possible outliers. After pre-processing and denoising, data was assessed with quality assurance plots to identify other potential outliers and was visually checked to control the quality of the segmentation and normalization in the brains of patients and healthy controls.

In these analyzes, rather than whole-brain analysis, specific seed regions of interest areas were placed and analyzed through connection correlations of these areas of interest with each other. Seed-to-voxel functional connectivity (FC) maps were created for each fMRI session (pre-surgery, post-surgery for patients with obesity, and control session for healthy controls). The focus is to examine the FC changes in the brain to correlate with the cognitive function alterations and reward bias. FC changes were examined in the medial prefrontal cortex, hippocampus, DMN, and dorsal attention network as cognitive ROIs. Dopaminergic pathways such as mesolimbic and mesocortical systems are important for reward-based learning. Therefore, FC between NAc, OFC, caudate, putamen, amygdala, insular cortex, and salience network was analyzed as regions of interest (ROI's). ROIs were selected from a set of default

pre-defined areas provided by the CONN toolbox. After the first level analysis, second-level analysis was conducted defining an uncorrected voxel-wise threshold of $p < 0.001$, FDR corrections at a cluster-size threshold of $p < 0.05$ were made for each a priori defined ROI.

Focused analyses on areas of interest mentioned above were performed both longitudinally (comparing 0 and 3 months of the individuals with obesity with each other) and baseline comparisons between the healthy controls and patient group with obesity. We also focused on functional changes in the cognitive networks and how they correlate with cognitive changes assessed by Penn-CNP after sleeve gastrectomy.

In the imaging studies, it is possible that the data quality may decrease as the participant moves their head during imaging. We had to exclude one person from the analysis as the data files were corrupted once it was uploaded to the CONN software.

2.4.2 Blood Biomarkers

Blood samples obtained were used to analyze peripheral biological markers that may be risk factors. Analysis were conducted at Koç University Laboratories.

Hemoglobin A1c (HbA1C) levels and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). In obesity, glucose metabolism is impaired in most cases. This may be in the stages of insulin resistance, prediabetes, or diabetes. It is thought to be related to possible mechanisms such as changes in intestinal hormones and an increase in bile acids after weight gain and bariatric surgery. HOMA-IR were calculated by using glucose and insulin results: (glucose (mg / dl) × insulin (pmol / L) / 405). HbA1c levels were measured using the High-performance liquid chromatography (HPLC) method in the Arkray HA 8160 instrument.

C-reactive protein (CRP) levels. Inflammation significantly modulates cognition. Accumulation of white adipose tissue in obesity enhances inflammation and increases plasma levels of CRP, which is a valid marker for inflammation in the blood (Ouchi, Parker, Lugus, & Walsh, 2011; Pohl, Woodside, & Luheshi, 2009), and weight loss after bariatric surgery is known to reduce CRP levels (Hawkins et al., 2015). CRP levels were measured using an immunoturbidimetric assay for in vitro quantification of CRP in human serum and plasma using Cobas c5 03 analyzers.

Vitamin B12, folic acid, ferritin levels. A decrease in these substances may occur due to less uptake and possible malabsorption in diet (Antoniewicz et al., 2019) A study shows that anemia was detected in %17, low ferritin in %15, and low B12 in 11 % of patients after one year of RYGB (Toh, 2009). Therefore, they should be followed routinely after bariatric surgery. The Electrochemiluminescence immunoassay (ECLIA) method was used for in vitro quantitative analysis of vitamin B12, ferritin, and folate levels via Cobas e 801 Analyzer.

Lipid panel (Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). Dyslipidemia, defined as increased total or LDL and decreased HDL cholesterol, is an important comorbidity of obesity and is a risk factor for cardiovascular diseases (Dixon & O'brien, 2002). Weight loss surgeries have improved abnormal lipid profiles seen in obesity. 3 months post-surgery, total cholesterol, LDL, triglyceride levels significantly decreased, and HDL levels increased (Tabasi et al., 2019). These changes continue to improve or remain stable 12-months post-surgery as well. Lipid panel variables were measured using a homogeneous enzymatic colorimetric test method for in vitro quantitative determination of LDL, HDL, total

cholesterol, and triglycerides in human plasma and serum on Roche/Hitachi Cobas c 503 Analyzer.

For the analysis of biochemical parameters, blood samples were taken in the morning after 8 hours of fasting. Blood samples were centrifuged at 3500 rpm, +40 ° C for 10 minutes, and serum and plasma will be separated. For all analyzes. 15-20 ml of blood were collected from the patients.

2.5 Statistical Analysis

The data from the scales were stored in a single database with the Qualtrics program and automatically transferred to the SPSS database. The Penn-CNP data was downloaded directly as an SPSS file. Descriptive statistics determined the psychiatric characteristics of the patients. Psychiatric symptomatology and stress reports determined by psychological scales were evaluated similarly. The changes in cognitive characteristics over time were monitored by Penn-CNP, and statistical analyses were done between dependent groups. Psychiatric symptomatology and stress factors determined by psychological scales were evaluated similarly. For all variables, first, normal distribution tests were performed with the Shapiro-Wilk normality test for continuous variables. Parametric tests (paired t-test) were selected for normally distributed variables, and non-parametric tests (Wilcoxon signed-rank test) were chosen for non-normally distributed variables to assess the within-group differences between pre-surgery and 3 months post-surgery. To compare baseline patients with obesity and healthy controls, Mann-Whitney U tests were performed for cognitive characteristics and psychiatric symptomatology. Non-parametric tests were preferred as the sample size of healthy controls was relatively small (n=15).

To determine which factors predicted the improvement in cognition, we used a linear mixed-effect model in Jamovi Version 1.6.15.0 to identify the predictor variables for each outcome variable (g factor, IFAC_TOT, DFACT_TOT, SVT, CPT_TP) where the outcome variable was regressed on a random effect variable for patients with obesity, defining BMI, HOMA-IR, CRP, and triglycerides as covariates and time as a fixed factor (pre-surgery, post-surgery).

For all analyses in the PRT task, calculations of "response bias" and "discriminability" were made for each block separately, and the overall performance. Previous literature on PRT trials with RT shorter than 150 ms and longer than 2500 ms were excluded, and after natural log transformation, outlier trials were excluded (mean ± 3SD). 10 patients' pre- and post-surgery results and 1 healthy control score were excluded after the quality control.

FC values for regions showing significant FC changes for comparing baseline and post-surgery in patients with obesity and for comparing baseline patients with obesity and healthy controls were extracted for each participant, and data were imported to SPSS as z scores for each seed ROI. Bivariate correlation analyses were carried out between the change in connectivity values and the change in z scores of pre-surgery and post-surgery values of "g" factor, IFAC_TOT, DFAC_TOT, SVT, CTP_TP, BMI, HOMA-IR, and CRP. The statistical significance threshold for all the analyses was set at $p < 0.05$. Koç University licensed SPSS program version 28 was used for statistical analysis.

Chapter 3:

RESULTS

Sociodemographic information of the SG patient group (n=42), whose 3rd-month evaluations were completed in terms of scales, are given in Table 3.1.

Among the 42 patients, 19 could be taken to fMRI. 15 healthy controls were matched to these 19 patients for age, gender, and education. The sociodemographic data of participant groups are listed in Table 3.1. No difference was observed among the groups for sociodemographic variables.

Table 3.1 Sociodemographic Variables of The Participant Groups

	Patient group with obesity (Mean ±SD)	Patient group with obesity for fMRI data (Mean ±SD)	Healthy control group (Mean ±SD)	p*	p**
Age	38.26 ± 9.00	35.32 ± 8.35	33.33 ± 10.47	0.068	0.410
Gender (F/M)	29 /13	17 / 2	13 / 2	0.307	1.00
Education (Highschool/ College and higher)	18 / 24	6 / 13	2 / 13	0.011	0.104
Diabetes (Yes/No)	7 / 35	2 / 17	0 / 15	0.172	0.492
Hypertension (Yes/No)	6 / 36	2 / 17	0 / 15	0.325	0.492

Psychiatric disorder (Yes/No)	7 / 35	3 / 16	0 / 15	0.172	0.238
Current psychiatric medication (Yes/No)	2 / 40	0 / 19	0 / 15	1.00	1.00

Note. *p value represents a comparison of patients with obesity and healthy controls (n=42 for patients with obesity, n=15 healthy controls). **p value represents comparison patients with obesity for fMRI and healthy controls (n=19 for patients with obesity for fMRI, n=15 healthy controls).

In the SG patient group, dysregulated metabolic function and elevated plasma levels of CRP as an inflammation marker were observed at pre-surgery assessment. Patients with obesity had significantly higher HOMA-IR, HbA1c, and CRP levels. They also had decreased HDL and increased triglycerides along with significantly increased ferritin compared to healthy controls (Table 3.2).

Table 3.2 Metabolic and inflammatory measurements in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Healthy controls (Mean ±SD)	p
BMI	43.33 ±5.54 (n=42)	21.34 ±1.59	<0.001
HOMA-IR	11.60 ±17.26 (n=37)	1.93 ±0.83	<0.001
HbA1c	5.74 ±0.44 (n=36)	5.28 ±0.19	<0.001
CRP	13.69 ±18.34 (n=38)	1.61 ±3.52	<0.001

CHOL	197.93 ±32.73 (n=39)	189.08 ±34.16	0.434
HDL	45.51 ±9.11 (n=40)	64.50 ±14.38	<0.001
LDL	137.44 ±34.82 (n=40)	129.76 ±36.32	0.479
TRIG	183.72 ±118.74 (n=40)	82.04 ±24.57	<0.001
B12 *	390.29 ±109.01 (n=38)	430.30 ±108.81	0.186
FERR *	146.31 ±157.71 (n=39)	83.60 ±98.91	0.028
FOL *	8.77 ±5.29 (n=40)	9.73 ±3.51	0.131

Note. Data were analyzed by Mann-Whitney U test. Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HbA1c, Hemoglobin A1c; CRP, C-Reactive Protein; CHOL, Total Cholesterol; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TRIG, Triglycerides; B12, Vitamin B12; FERR, Ferritin; FOL, Folate (n=15 for healthy controls).

Correlating with weight loss, metabolic parameters: BMI, HOMA-IR, HbA1C, and CRP levels significantly decreased at the 3rd-month post-surgery (Table 3.3). In terms of the lipid panel, total cholesterol and triglyceride levels were significantly reduced, without changing HDL and LDL levels, at 3 months post-surgery. B12 increased significantly while ferritin and folic acid levels did not change 3 months post-surgery, which could be due to recommended vitamin supplementation after surgery.

Table 3.3 Metabolic and inflammatory measurements in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
BMI (n=42)	43.33 ±5.54	34.69 ±4.76	<0.001
HOMA-IR (n=34)	11.72 ±17.98	2.88 ±1.96	0.007
HbA1c (n=31)	5.69 ±0.34	5.21 ±0.28	<0.001
CRP * (n=29)	13.69 ±18.34	5.72 ±9.24	<0.001
CHOL (n=31)	200.87 ±33.57	186.01 ±42.85	0.040
HDL (n=34)	47.29 ±8.10	46.92 ±8.00	0.799
LDL (n=36)	139.79 ±32.55	131.21 ±31.32	0.123
TRIG (n=34)	160.79 ±82.39	107.44 ±37.90	<0.001
B12 * (n=34)	390.29 ±109.01	442.88 ±183.74	0.045

FERR * (n=34)	146.31 ±157.71	112.98 ±116.19	0.059
FOL * (n=32)	8.77 ±5.29	6.93 ±3.62	0.117

Note. Data were analyzed by Paired T-Test and Wilcoxon Signed Rank Test (*).

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HbA1c, Hemoglobin A1c; CRP, C-Reactive Protein; CHOL, Total Cholesterol; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TRIG, Triglycerides; B12, Vitamin B12; FERR, Ferritin; FOL, Folate.

3.1 Psychiatric Symptomatology and Stress Reports Before and After Sleeve Gastrectomy

In the patient group with obesity, childhood trauma was significantly higher than healthy controls, along with depression and anxiety scores at baseline, which were higher in the group with obesity although not statistically significant (Table 3.4).

Table 3.4 Self-assessment scales in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Healthy controls (Mean ±SD)	p
CTQ	35.10 ±9.74	29.93 ±6.15	0.025
DT	5.49 ±2.00	5.67 ±1.80	0.967
CSS	22.48 ±11.57	16.73 ±7.32	0.092

PSS	24.24 ±6.70	22.00 ±3.96	0.288
MSPSS	5.61 ±1.32	5.60 ±1.16	0.831
Beck-Dep	10.24 ±7.41	6.20 ±4.68	0.049
Beck-Anx	9.00 ±9.12	6.40 ±6.08	0.322
CFQ	20.69 ±12.12	22.93 ±12.27	0.479
BIS	56.36 ±9.44	54.47 ±7.37	0.561
SHAPS	1.85 ±3.47	0.40 ±0.91	0.098
SHAPS (Yes/No) **	7/32	1/14	0.419
MDQ (Yes/No) **	9/32	1/14	0.259

Note. Data were analyzed by Mann-Whitney U test and Chi-Squared test (**).Abbreviations: SD, Standard Deviation; CTQ, Childhood Trauma Questionnaire; DT, Distress Thermometer; CSS, Chronic Stress Scale; PSS, Perceived Stress Scale; MSPSS, Multidimensional Scale of Perceived Social Support; Beck-Dep, Beck Depression Inventory; Beck-Anx, Beck Anxiety Inventory; CFQ, Cognitive Failures Questionnaire; BIS, Barratt Impulsivity Scale; SHAPS, Snaith-Hamilton Pleasure Scale; MDQ, Mood Disorder Questionnaire (n=42 for patients with obesity, n=15 for healthy controls).

Depression, anxiety, impulsivity, stress, cognitive symptoms, and anhedonia scores evaluated by self-report scales did not change significantly at the 3rd-month assessment compared to pre-surgery in the SG patient group (Table 3.5). The Perceived Stress Scale score decreased significantly; however, after multiple comparison corrections, this analysis has also become insignificant. Both depression and anxiety scores showed a trend towards improvement after

surgery, although non-significant. Contrary to our hypothesis, the "Cognitive Failures Questionnaire" did not change between pre-surgery and 3 months post-surgery.

Table 3.5 Self-assessment scales in patients with obesity 'pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
DT	5.49 ±2.00	4.98 ±2.14	0.179
CSS	22.48 ±11.57	21.02 ±10.79	0.249
PSS *	24.24 ±6.70	21.85 ±7.51	0.037
MSPSS *	5.61 ±1.32	5.45 ±1.80	0.950
Beck-Dep	10.24 ±7.41	8.26 ±5.05	0.092
Beck-Anx	9.00 ±9.12	7.69 ±6.96	0.092
CFQ *	20.69 ±12.12	21.43 ±10.38	0.461
BIS *	56.36 ±9.44	56.05 ±9.24	0.793
SHAPS	1.85 ±3.47	1.68 ±2.893	0.871
SHAPS (Yes/No) **	7/31	9/29	1.000
MDQ (Yes/No) **	1/37	1/37	1.000

Note. Data were analyzed by Paired T-Test, Wilcoxon Signed Rank test (*) and Chi-Squared test (**). Abbreviations: SD, Standard Deviation; DT, Distress Thermometer; CSS, Chronic Stress Scale; PSS, Perceived Stress Scale; MSPSS, Multidimensional Scale of Perceived Social Support; Beck-Dep, Beck Depression Inventory; Beck-Anx, Beck Anxiety Inventory;

CFQ, Cognitive Failures Questionnaire; BIS, Barratt Impulsivity Scale; SHAPS, Snaith-Hamilton Pleasure Scale; MDQ, Mood Disorder Questionnaire (n=42).

3.2 Cognitive Function Before and After Sleeve Gastrectomy

According to the Penn-CNP neuropsychological test battery results, for the "g" factor, which represents the overall task performance of the Penn-CNP battery, there was a significant increase of "g" scores at 3 months post-surgery (Table 3.6), supporting a general cognitive improvement independent of specific domains.

Table 3.6 PENN-CNP "G" Factor in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
G Factor	-0.17 ±0.81	0.29 ±1.07	<0.001

Note. Data were analyzed by Wilcoxon Signed Rank test (n=34).

When subdomains of cognitive assessment were investigated further, a statistically significant increase was detected especially in the results of memory tasks. Below is a comparison of the pre-operative and post-operative measurements of the two Penn-CNP Face Memory tasks for SG surgery participants (Table 3.7, 3.8).

Table 3.7 PENN-CNP Face Memory Test in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
CPF_TP	17.42 ±1.69	18.05 ±1.86	0.043
CPF_TN	15.11 ±3.27	17.16 ±3.31	<0.001
CPF_FP	4.89 ±3.27	2.84 ±3.31	<0.001
CPF_FN	2.58 ±1.69	1.95 ±1.86	0.043
IFAC_TOT	32.53 ±3.37	35.21 ±3.80	<0.001

Note. Data were analyzed by Wilcoxon Signed Rank test (n=38).

According to this analysis, the false-positive and false-negative response scores of the participants decreased significantly, and the true-negative and true-positive response scores increased significantly. In the delayed version of the same task, the false-positive and false-negative response scores of the participants decreased significantly, and the true-positive and true-negative response scores increased significantly (Table 3.7, 3.8).

Table 3.8 PENN-CNP Face Memory Test Delayed in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
CPFD_TP	17.87 ±1.97	18.82 ±1.51	0.006
CPFD_TN	16.11 ±3.43	17.11 ±3.14	0.032

CPFD_FP	3.89 ±3.43	2.89 ±3.14	0.032
CPFD_FN	2.13 ±1.98	1.18 ±1.51	0.006
CPFD. IFAC_TOT	33.97 ±3.59	35.92 ±3.58	0.001

Note. Data were analyzed by Wilcoxon Signed Rank test (n=38).

Also, in the Visual Object Learning task, total response scores and true-positive response scores increased significantly at 3 months post-surgery (Table 3.9). The delayed version of this task did not change between assessments (Table 3.10).

Table 3.9 PENN-CNP Visual Object Learning in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
SVT	15.13 ±2.69	16.10 ±2.45	0.002
SVT_TP	7.98 ±1.61	8.36 ±1.54	0.044
SVT_TN	7.15 ±2.34	7.74 ±1.71	0.098
SVT_FP	2.85 ±2.34	2.26 ±1.71	0.098
SVT_FN	2.00 ±1.62	1.64 ±1.55	0.053

Note. Data were analyzed by Wilcoxon Signed Rank test (n=39).

Table 3.10 PENN-CNP Visual Object Learning Delayed in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
SVTD	15.30 ±2.76	15.10 ±2.05	0.334
SVTD_TP	8.55 ±1.48	8.44 ±1.48	0.756
SVTD_TN	6.75 ±2.59	6.67 ±2.20	0.572
SVTD_FP	3.25 ±2.59	3.33 ±2.20	0.572
SVTD_FN	1.45 ±1.48	1.56 ±1.48	0.756

Note. Data were analyzed by Wilcoxon Signed Rank test (n=39).

There was also a significant change in the results of the visual attention and impulsivity test (Table 3.11). In the Continuous Performance task, true-positive response scores increased significantly, and false-negative response scores decreased significantly for the total assessment and sub-parts. SG patients showed significant improvement in these tasks at 3 months post-surgery indicating better cognitive abilities.

Table 3.11 PENN-CNP Continuous Performance Test in patients with obesity 'pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
CPN_TP	53.74 ±8.81	57.18 ±4.74	0.005
CPN_FP	4.26 ±3.28	3.76 ±3.81	0.195

CPN_TN	115.74 ±3.28	116.24 ±3.81	0.195
CPN_FN	6.26 ±8.81	2.82 ±4.75	0.005
CPL_TP	56.03 ±6.04	57.38 ±2.78	0.177
CPL_FP	7.91 ±5.45	6.94 ±5.92	0.285
CPL_TN	112.09 ±5.45	113.06 ±5.92	0.285
CPL_FN	3.97 ±6.04	2.62 ±2.79	0.177
CPT_TP	109.76 ±12.18	114.56 ±6.75	0.002
CPT_FP	12.18 ±7.24	10.35 ±7.52	0.055
CPT_TN	227.82 ±7.24	229.29 ±7.44	0.051
CPT_FN	10.24 ±12.18	5.79 ±6.93	0.006

Note. Data were analyzed by Wilcoxon Signed Rank test (n=34).

There were no differences in tasks related to working memory (Table 3.12) and executive function (Table 3.13) between pre-surgery and 3 months post-surgery.

Table 3.12 PENN-CNP Letter-N-Back in patients with obesity ,pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
LNB_TP	42.16 ±2.68	42.35 ±2.53	0.595
LNB_FP	0.86 ±1.74	0.95 ±1.68	0.618

LNB_TP2	13.03 ±2.25	13.30 ±1.91	0.339
LNB_FP2	0.30 ±1.18	0.22 ±0.53	0.710

Note. Data were analyzed by Wilcoxon Signed Rank test (n=37).

Table 3.13 PENN-CNP Conditional Exclusion Test in patients with obesity 'pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
PCET_CR	38.87 ±8.67	37.47 ±9.05	0.623
PCET_ER	37.61 ±16.56	33.92 ±14.89	0.232
PCET_PER_ER	19.66 ±11.43	17.82 ±10.34	0.257
PCET_PER_RES	21.63 ±12.76	19.50 ±11.37	0.238

Note. Data were analyzed by Wilcoxon Signed Rank test (n=38).

There was no difference between SG patients at baseline and healthy controls at the results of the individual tasks (Table 3.15, 3.16, 3.17, 3.18, 3.19, 3.20) and the overall performance, "g" factor, in Penn-CNP (Table 3.14). The only difference was observed in the Continuous Performance test, where healthy controls had lowered false-positive response scores and higher true-negative response scores for a sub-part in the continuous performance task compared to the group with obesity (Table 3.21).

Table 3.14 PENN-CNP "G" Factor in patients with obesity and controls.

	Patients with obesity (Mean ±SD) (n=35)	Controls (Mean ±SD) (n=14)	p
G Factor	-0.17 ±0.82	-0.29 ±1.19	0.803

Not. Data were analyzed by Mann Whitney U test (n=34 for patients with obesity, n=14 for healthy controls).

Table 3.15 PENN-CNP Face Memory Test in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Healthy controls (Mean ±SD)	p
CPF_TP	17.42 ±1.69	16.73 ±2.76	0.520
CPF_TN	15.11 ±3.27	15.93 ±3.95	0.241
CPF_FP	4.89 ±3.27	4.07 ±3.95	0.241
CPF_FN	2.58 ±1.69	3.27 ±2.76	0.520
IFAC_TOT	32.53 ±3.37	32.67 ±3.37	0.984

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=15 for healthy controls).

Table 3.16 PENN-CNP Face Memory Test Delayed in patients with obesity and controls.

	Patients with obesity (Mean ±SD) (n=38)	Controls (Mean ±SD) (n=15)	p
CPFD_TP	17.87 ±1.97	16.93 ±2.58	0.141
CPFD_TN	16.11 ±3.43	17.20 ±3.45	0.155
CPFD_FP	3.89 ±3.43	2.80 ±3.45	0.155
CPFD_FN	2.13 ±1.98	3.07 ±2.58	0.141
CPFD. IFAC_TOT	33.97 ±3.59	34.13 ±3.52	0.992

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=15 for healthy controls).

Table 3.17 PENN-CNP Visual Object Learning in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Controls (Mean ±SD)	p
SVT	15.26 ±2.59	16.13 ±2.53	0.112
SVT_TP	7.92 ±1.60	8.00 ±1.31	0.889
SVT_TN	7.33 ±2.06	8.13 ±2.10	0.110
SVT_FP	2.67 ±2.06	1.87 ±2.10	0.110
SVT_FN	2.05 ±1.61	2.00 ±1.30	0.819

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=15 for healthy controls).

Table 3.18 PENN-CNP Visual Object Learning Delayed in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Controls (Mean ±SD)	p
SVTD	15.44 ±2.65	15.27 ±2.49	0.852
SVTD_TP	8.51 ±1.48	7.87 ±1.64	0.158
SVTD_TN	6.92 ±2.38	7.40 ±1.80	0.482
SVTD_FP	3.08 ±2.38	2.60 ±1.80	0.482
SVTD_FN	1.49 ±1.48	2.13 ±1.64	0.158

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=14 for healthy controls).

Table 3.19 PENN-CNP Letter-N-Back in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Controls (Mean ±SD)	P
LNB_TP	42.18 ±2.65	42.47 ±2.67	0.617
LNB_FP	0.84 ±1.72	1.00 ±1.46	0.774
LNB_TP2	13.03 ±2.22	13.27 ±1.83	0.913
LNB_FP2	0.29 ±1.16	0.47 ±0.91	0.304

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=15 for healthy controls).

Table 3.20 PENN-CNP Conditional Exclusion Test in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Controls (Mean ±SD)	p
PCET_CR	37.87 ±8.67	38.87 ±9.78	0.671
PCET_ER	37.61 ±16.56	35.87 ±15.70	0.759
PCET_PER_ER	19.66 ±11.43	18.60 ±11.93	0.649
PCET_PER_RES	21.63 ±12.76	21.13 ±13.15	0.953

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=15 for healthy controls).

Table 3.21 PENN-CNP Continuous Performance Test in patients with obesity and controls.

	Patients with obesity (Mean ±SD)	Controls (Mean ±SD)	p
CPN_TP	53.78 ±8.49	53.50 ±10.82	0.515
CPN_FP	4.19 ±3.26	2.86 ±2.51	0.198
CPN_TN	115.81 ±3.26	117.14 ±2.51	0.198
CPN_FN	6.22 ±8.49	6.50 ±10.82	0.515
CPL_TP	55.30 ±6.96	52.71 ±10.24	0.244

CPL_FP	7.97 ±5.66	4.07 ±3.69	0.011
CPL_TN	112.03 ±5.65	115.93 ±3.69	0.011
CPL_FN	4.70 ±6.96	7.29 ±10.24	0.244
CPT_TP	109.08 ±12.49	106.21 ±20.50	0.882
CPT_FP	12.16 ±7.56	7.21 ±5.19	0.026
CPT_TN	227.84 ±7.56	233.07 ±5.33	0.017
CPT_FN	10.92 ±12.49	13.50 ±20.64	0.958

Note. Data were analyzed by Mann Whitney U test (n=38 for patients with obesity, n=14 for healthy controls).

3.3 Reward Response Bias Before and After Sleeve Gastrectomy

The raw data obtained in this task was subjected to the quality control evaluation based on the task application features and participant responses, and the data that did not pass the quality standards were excluded from the study. For this reason, results of 32 patients are presented. In the SG patient group, there was no significant difference in the postoperative 3rd month in terms of reward bias and discriminability variables, which are the main outputs of the PRT, compared to the preoperative period (Table 3.22).

Table 3.22 Response bias (RB) and discriminability scores of Probabilistic Reward Task (PRT) in patients with obesity pre-surgery and 3 months post-surgery.

	Pre-Surgery (Mean ±SD)	3rd Month (Mean ±SD)	p
Response Bias_Main	0.147 ±0.187	0.173 ±0.185	0.603
Response Bias_Total	0.135 ±0.249	0.152 ±0.157	0.776
Discriminability_ Main	0.275 ±0.178	0.284 ±0. 176	0.772
Discriminability_ Total	0.253 ±0.168	0.272 ±0.171	0.438

Note. Data were analyzed by Paired T-test (n =32).

When the SG patient group at baseline was compared with the healthy control group, a significant difference was found between the two groups in terms of reward bias (Table 3.23). SG patients had greater response bias scores compared to controls both in the total task and in the main parts (2nd and 3rd blocks) of PRT. These results are in line with our hypothesis that patients with obesity have greater reward bias compared to controls.

Table 3.23 Response bias (RB) and discriminability scores of Probabilistic Reward Task (PRT) in patients with obesity and controls

	Patients with obesity (Mean ±SD) (n=40)	Healthy controls (Mean ±SD) (n=14)	p
Response Bias_Main	0.157 ±0.172	0.08 ±0.174	0.012
Response Bias_Total	0.144 ±0.225	0.072 ±0.149	0.022
Discriminability_ Main	0.264 ±0.175	0.346 ±0. 114	0.097
Discriminability_ Total	0.248 ±0.159	0.206 ±0.090	0.261

Note. Data were analyzed by Mann-Whitney U test (n=40 for patients with obesity, n=14 for controls).

3.4 Brain Functional Connectivity Changes After Sleeve Gastrectomy

3.4.1 3-months Post-Surgery > Pre-Surgery.

Post-surgery, SG patients had greater connectivity between the left frontal orbital cortex (OFC) and the left middle and inferior frontal gyrus (Table 3.24, Figure 3.1a). They had greater connectivity between the left amygdala and subcallosal cortex/ left OFC (Figure 3.1b) and

between the left hippocampus and precuneus cortex (Figure 3.1c). Main reward regions such as NAc, caudate, and putamen failed to show significant connectivity differences.

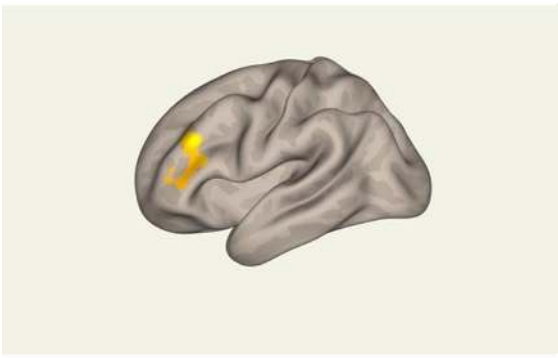
In terms of network connectivity, none of the regions of the DMN showed connectivity changes. In the salience network, SG patients had lower connectivity between the right rostral prefrontal cortex (RPFC) and left superior parietal lobule and between the left supramarginal gyrus (SMG) and the left superior temporal gyrus at post-surgery compared to pre-surgery (Figure 3.1e). Although, within the network, anterior insula region connectivity did not change, when the insular cortex was used as seed ROI, greater connectivity between the right insular cortex and right middle temporal gyrus was observed (Figure 3.1d). In the dorsal attention network, SG patients had lower connectivity between the right frontal eye field (FEF) and right frontal pole and greater connectivity between the right FEF and precuneus cortex/ cingulate gyrus post-surgery (Figure 3.1f).

Table 3.24 Significant seed-to-target changes in functional connectivity in patients with obesity ' pre-surgery and 3 months post-surgery.

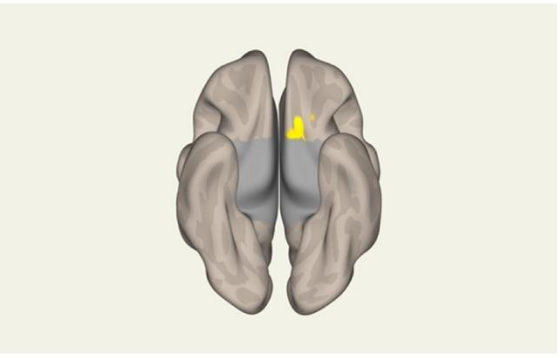
Seed ROI	Target ROI	Cluster size	x, y, z	p-FWE	p-FDR	p-unc	Improve-ment
Frontal Orbital Cortex L	Middle Frontal Gyrus L/ Inferior Frontal Gyrus L	251	-46, +30, +26	0.00055	0.000063	0.00001	Greater
Insular Cortex R	Middle Temporal Gyrus R	182	+60, -52, +00	0.000744	0.000834	0.000019	Lower

Amygdala L	Frontal Orbital Cortex L	97	-12, +18, -12	0.025140	0.024721	0.000634	Greater
Hippocampus L	Precuneus Cortex	106	-10, -68, +36	0.021338	0.027519	0.000573	Greater
Salience. RPFC R	Superior Parietal Lobule L	134	-24, -50, +52	0.006335	0.009195	0.000170	Lower
Salience. SMG L	Planum Temporal L/ Superior Temporal Gyrus L	169	-64, -18, +02	0.001698	0.000931	0.000047	Lower
Dorsal Attention. FEF R	Frontal Pole Right	137	+40, +38, +08	0.006540	0.007258	0.000181	Lower
Dorsal Attention. FEF R	Precuneous Cortex/ Cingulate Gyrus	84	+16, -52, +28	0.069582	0.039893	0.001995	Greater

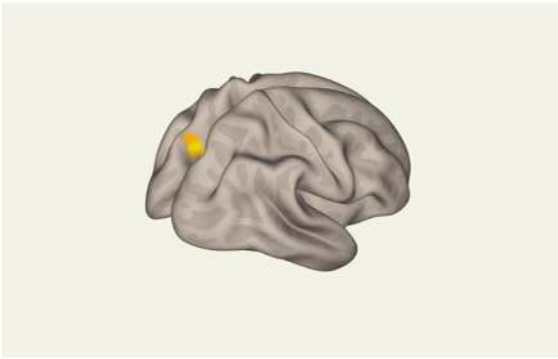
Note. Post-surgery > Pre-surgery. Abbreviations: RPFC, Right Rostral Prefrontal Cortex; SMG, Supramarginal Gyrus; FEF, Frontal Eye Field; L, Left; R, Right.



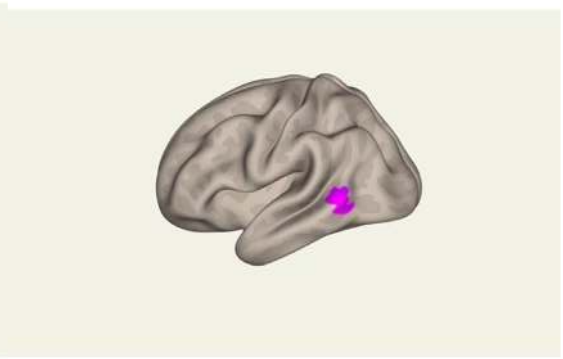
(a) L OFC – L Middle and Inferior Frontal Gyrus



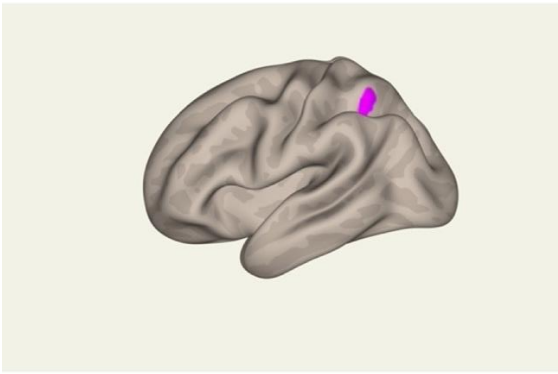
(b) L Amygdala – L OFC, Subcallosal Cortex



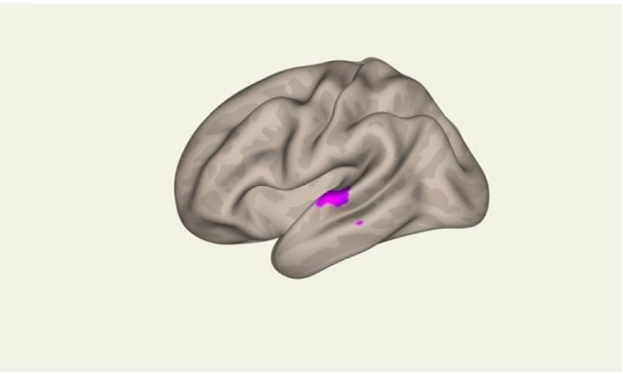
(c) L Hippocampus – Precuneus Cortex



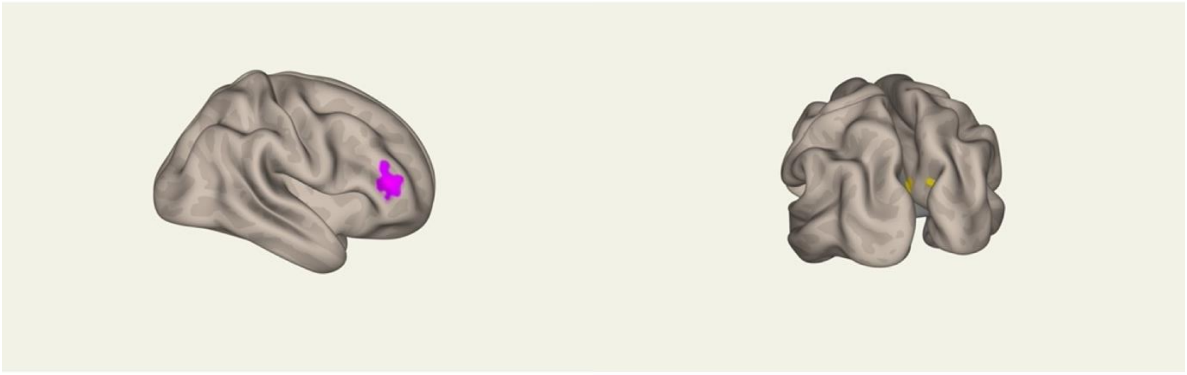
(d) R Insula – R Middle Temporal Gyrus



(e) R RPFC – L Superior Parietal Lobule



L SMG – L Superior Temporal Gyrus



(f) R FEF – R Frontal Pole *R FEF – Precuneus Cortex, Cingulate Gyrus Posterior*

Figure 3.1 Significant voxels of altered functional connectivity between 3 months post-surgery and pre-surgery (n=19, cluster threshold p < 0.05, cluster-size p-FDR corrected, voxel-wise threshold p < 0.001, uncorrected). (a) Increased FC with the left frontal orbital cortex seed. (b) Increased FC with the left amygdala seed. (c) Increased FC with the left hippocampus seed. (d) Decreased FC with the right insular cortex seed. (e) Contrast of salience network between pre-surgery and 3 months post-surgery. (f) Contrast of dorsal attention network between pre-surgery and 3 months post-surgery.

3.4.2 Patients with Obesity > Healthy Controls; Pre-Surgery.

SG patients had lower connectivity between left putamen and left middle frontal gyrus/ superior frontal gyrus, left putamen and right cerebellum 6, right putamen and right superior frontal gyrus/ frontal pole, right putamen, and right middle frontal gyrus compared to controls (Table 3.25, Figure 3.2a). There were no changes in FC in areas of NAc and caudate. They had lower connectivity between right OFC and left lingual gyrus/ intracalcarine cortex, left OFC and left frontal pole/ OFC, and greater connectivity between right postcentral gyrus/ precentral gyrus (Figure 3.2b).

They had lower connectivity between the left amygdala and left superior parietal lobule/ lateral occipital cortex (Figure 3.2c) and greater connectivity between the right hippocampus and right

putamen/ insular cortex left hippocampus and right inferior frontal gyrus/ precentral gyrus and greater connectivity between left hippocampus and putamen (Figure 3.2d).

In the DMN, SG patients had greater connectivity between the medial prefrontal cortex (mPFC) and the right middle frontal gyrus compared to controls (Figure 3.2e). In the salience network, SG patients had increased connectivity between the right anterior insula and the right middle temporal gyrus/ SMG right, had greater connectivity between the right RPFC and the left planum temporal/ parietal operculum cortex/ SMG, and between the right RPFC and the left frontal pole. SG patients had higher connectivity between the left SMG and the planum temporal left/ parietal operculum cortex/ central operculum cortex (Figure 3.2g). When the insula is assessed separately as a seed ROI, SG patients showed greater connectivity between the right insular cortex and the right insular cortex/ OFC (Figure 3.2h). In the dorsal attention network, SG patients had greater connectivity between the right intraparietal sulcus (IPS) and the right postcentral gyrus (Figure 3.2f).

Table 3.25 Significant seed-to-target changes in functional connectivity in patients with obesity and controls.

Seed ROI	Target ROI	Cluster size	x, y, z	p-FWE	p-FDR	p-unc	Improvement
Putamen L	Middle Frontal Gyrus L/ Superior Frontal Gyrus L	155	-26, +14, +34	0.003714	0.00435 6	0.000106	Decrease

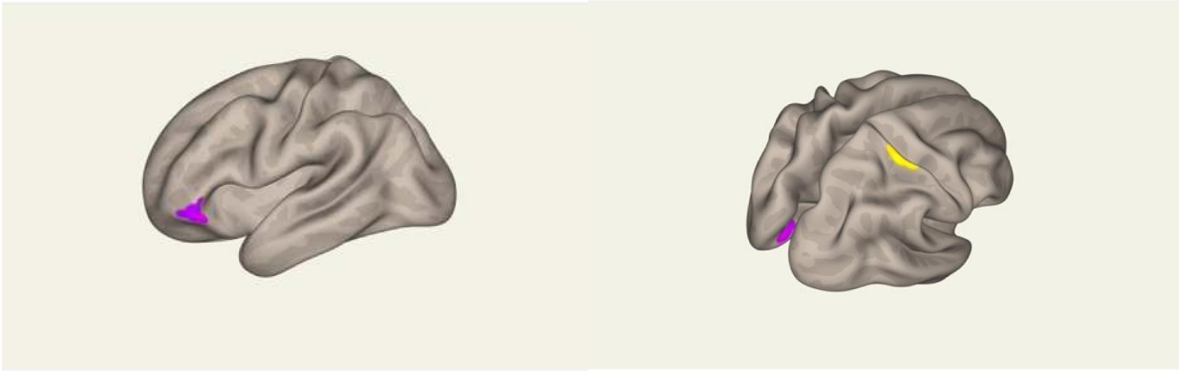
Putamen L	Cerebelum 6 R	93	+24, -64, -22	0.050847	0.03054 6	0.001490	Decrease
Putamen R	Superior Frontal Gyrus R/ Frontal Pole R	429	+10, +36, +50	0.00001	0.00000 1	0.000000	Decrease
Putamen R	Cerebelum 6 R	117	+22, -72, -28	0.019938	0.01243 6	0.000051	Decrease
Putamen R	Middle Frontal Gyrus R	82	+32, +18, +44	0.092090	0.03976 9	0.000002	Decrease
Frontal Orbital Cortex L	Frontal Pole Left/ Frontal Orbital Cortex L	129	-52, +30, -14	0.010887	0.00942 7	0.000314	Decrease
Frontal Orbital Cortex R	Lingual Gyrus L/ Intracalcarine Cortex L	181	-08, -82, -06	0.001824	0.00306 3	0.000055	Decrease
Frontal Orbital Cortex R	Postcentral Gyrus R/ Precentral Gyrus R	121	+38, -32, +64	0.018242	0.01543 8	0.000551	Increase

Insular Cortex R	Insular Cortex R/ Frontal Orbital Cortex R	168	+26, +12, -16	0.002996	0.00279 6	0.000090	Increase
Amygdala L	Superior Parietal Lobule L/ Lateral Occipital Cortex L	146	-12, -56, +66	0.004845	0.00790 2	0.000136	Decrease
Hippocampus R	Putamen/ Insular Cortex R	167	+28, -22, -02	0.002456	0.00460 5	0.000071	Increase
Hippocampus L	Inferior Frontal Gyrus R/ Precentral gyrus R	161	+60, +20, +12	0.003084	0.00462 6	0.000089	Increase
Hippocampus L	Putamen	105	+32, -18, -08	0.030720	0.01628 8	0.000899	Increase
Hippocampus L	Brainstem	104	-10, -26, -44	0.032098	0.01628 8	0.000940	Decrease
Hippocampus L	Thalamus R	79	+16, -28, +08	0.099527	0.03925 4	0.003020	Increase

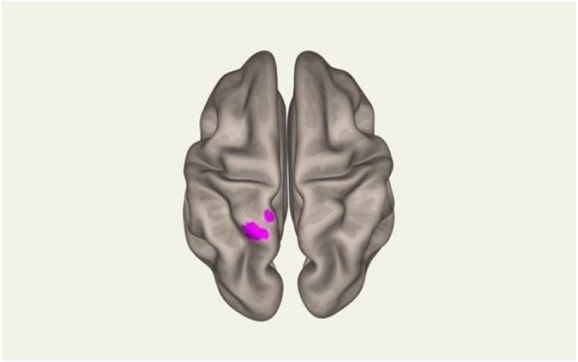
DMN. mPFC	Middle Frontal Gyrus R	124	+52, +30, +34	0.018479	0.028839	0.000577	Increase
Salience. Anterior Insula R	Middle Temporal Gyrus R/ Supramarginal Gyrus R	140	+54, -38, +06	0.011659	0.013909	0.000376	Increase
Salience. RPFC R	Planum Temporal L/ Parietal Operculum Cortex L/ SMG L	169	-50, -42, +18	0.003876	0.002219	0.000123	Increase
Salience. RPFC R	Frontal Pole L	87	-16, +58, +24	0.092569	0.027755	0.003084	Increase
Salience. SMG L	Planum Temporal L/ Parietal Operculum Cortex L	202	-56, -24, +10	0.001258	0.000680	0.000040	Increase
Dorsal Attention. IPS R	Postcentral Gyrus R	139	+58, -14, +48	0.012095	0.019895	0.000390	Increase

Note. Case/ Control> Control/ Case; Pre-surgery. Abbreviations: DMN, Default Mode Network; mPFC, Medial Prefrontal Cortex; RPFC, Right Rostral Prefrontal Cortex; SMG, Supramarginal Gyrus; FEF, Frontal Eye Field, L, Left; R, Right.

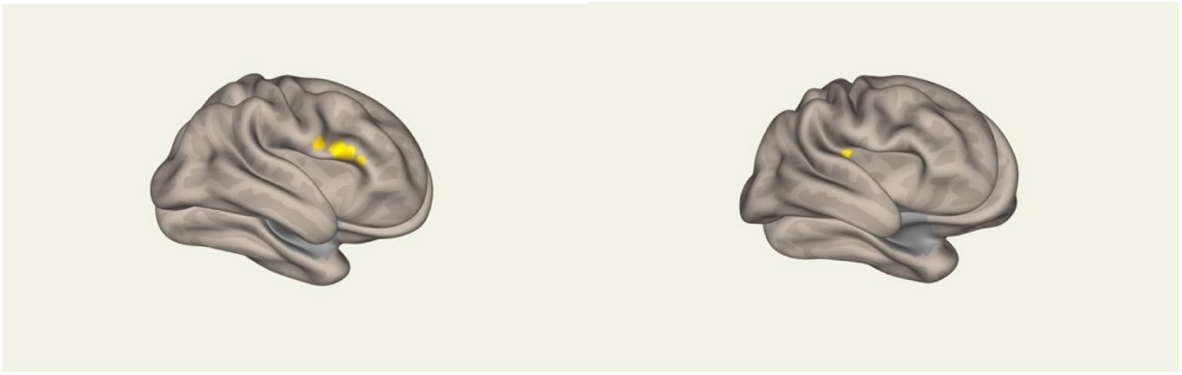
(a) L Putamen – L Middle / Superior Frontal Gyrus R Putamen – R Superior / Middle Frontal Gyrus



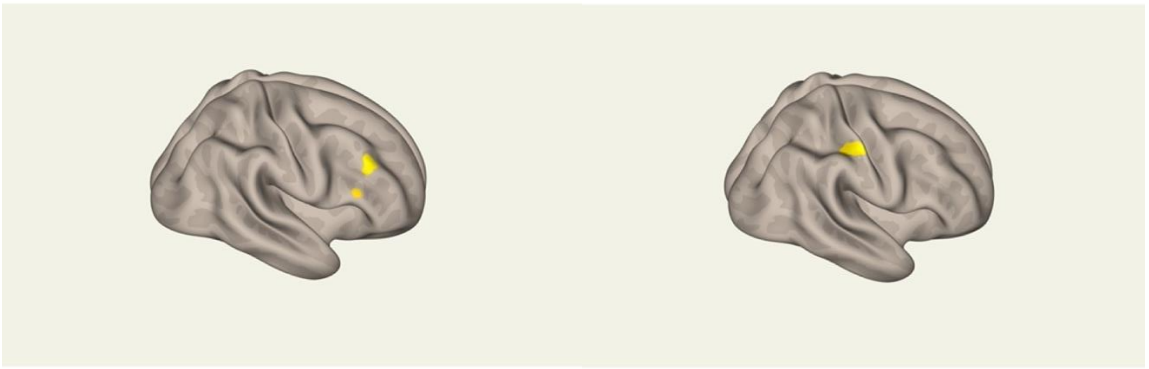
(b) L OFC – L OFC, Frontal pole *R OFC – L lingual Gyrus // R Postcentral Gyrus*



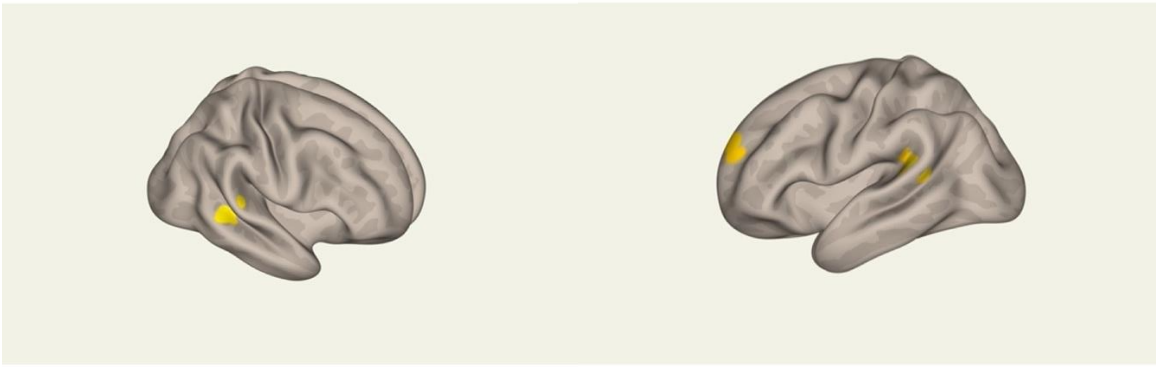
(c) L Amygdala – L Superior Parietal Lobule, Precuneus



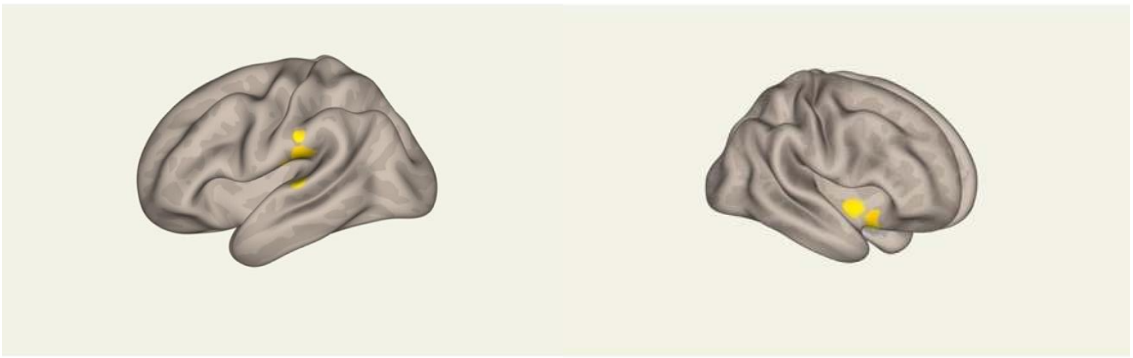
(d) L Hippo- R Inferior Frontal Gyrus // R Putamen *R Hippo – R Putamen, Insular Cortex*



(e) *mPFC – Middle Frontal Gyrus* *(f) R IPS – R Postcentral Gyrus*



(g) R A.Insula – R Middle and SMG Temporal Gyrus *R RPFC – L Planum Temporale, L SMG*



(g) L SMG – L Planum Temporale, L Parietal Operculum (h) R Insular Cortex – R Insular Cortex // R OFC

Figure 3.2 Significant voxels of altered functional connectivity between patients with obesity (n=19) and healthy controls (n=15). With the right IPS seed. (Cluster threshold $p < 0.05$, cluster-size p-FDR corrected, voxel-wise threshold $p < 0.001$, uncorrected). (a) Decreased FC with the putamen seed. (b) Decreased and increased FC with the frontal orbital cortex seed. (c) Decreased FC with the left amygdala seed. (d) Increased FC with the hippocampus seed. (e) Contrast of default mode network (DMN). (f) Contrast of dorsal attention network. (g) Contrast of salience network. Figure (h) Increased FC with the right insular cortex seed.

3.4.3 Correlations between 3 Months Post-Surgery > Pre-surgery Functional Connectivity Changes and Cognitive and Metabolic Variables.

BMI, HOMA-IR, HbA1C, and CRP levels significantly decreased at the 3rd-month post-surgery (Table 3.3). Total cholesterol and triglyceride levels were also improved at 3 months.

Mixed-effects regression was carried out in Jamovi defining BMI, HOMA-IR, CRP, and triglycerides as covariates and time as a factor (pre-surgery, post-surgery) to examine the possible predictor role of these metabolic and inflammatory markers in the observed cognitive improvement. When “g” factor, total response scores in the face memory task (IFAC_TOT), total response scores in the face memory task delayed (DFAC_TOT), total response scores in the visual object learning task (SVT), and total true-positive response scores in continuous performance task (CTP_TP) were defined as dependent variables, the results of the regression analysis revealed that the model was a significant predictor of SVT, however other models were

insignificant (Table 3.26). BMI negatively predicted SVT (B=-0.7356, p<0.001), while other scores did not. None of the variables had a predictor effect on any of the tasks in Penn-CNP.

	G SCORE			IFAC_TOT			DFAC_TOT			SVT			CPT_TP		
	B	95% CI	p	B	95% CI	p	B	95% CI	p	B	95% CI	p	B	95% CI	p
Intercept	-0,059	-0.0379 to 0.261	0,719	33,759	32.66 to 34.85	<0.001	34,769	33.689 to 35.848	<0.001	15,5408	14.761 ro 16.322	<0.001	111,06	107.958 to 114.159	<0.001
Time	0,291	-0.406 to 0.988	0,417	2,304	-0.031 to 4.640	0,059	0,079	-2.224 to 2.381	0,947	-0,7356	-2.083 to 0.612	0.289	7.481	-0.133 to 15.095	0,06
BMI	-0,013	-0.081 to 0.054	0,696	-0,043	-0.274 to 0.188	0,719	-0,117	-0.332 to 0.098	0,293	-0,1887	-0.323 to -0.055	0.008	0,18	-0.416 to 0.776	0,558
HOMAIR	-0,007	-0.016 to 0.010	0,344	0,014	-0.033 to 0.061	0,568	-0,047	-0.105 to 0.013	0,13	0,0108	-0.012 to 0.034	0.359	0,096	-0.123 to 0.316	0,394
CRP	-0,003	-0.007 to 0.016	0,656	0,007	-0.039 to 0.053	0,773	-0,014	-0.068 to 0.0398	0,613	-0,0252	-0.049 to -0.002	0.044	0,027	-0.157 to 0.212	0,772
TRIG	-9.11e−4	-0.003 to 0.02	0,464	-0,004	-0.012 to 0.005	0,386	-0,006	-0.016 to 0.003	0,175	-3.22e−4	-0.005 to 0.004	0.893	-0,003	-0.033 to 0.027	0,846
Random parts															
AIC		145.463			304.316			323.236			252.220			452.695	
R2 marginal		0.103			0.153			0.167			0.173			0.0777	
R2 conditional		0.764			0.772			0.642			0.905			0.2545	
Number of observations		54			60			60			62			58	
Groups		27			30			30			31			29	
ICC		0.737			0.731			0.570			0.885			0.192	

Table 3.26 Mixed effects regression models to assess predictors of cognitive improvement.

There was a negative correlation between the change in total correct responses in the face memory task (IFAC_TOT) and the right RPFC in the salience network (r=-0.502, n=18, p=0.034) (Figure 3.3). All other significant regions mentioned above and the cognitive ("g" factor, DFAC_TOT, SVT, CTP_TP) and metabolic parameters (BMI, HOMA-IR, CRP) did not correlate with each other.

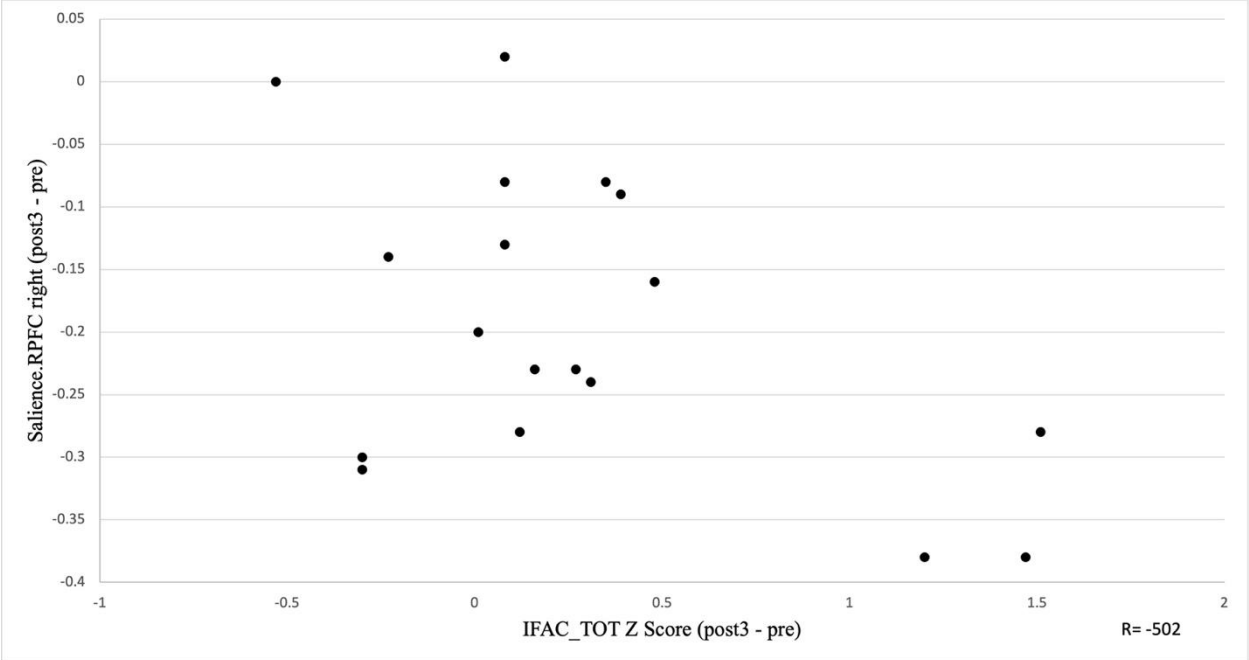


Figure 3.3 Correlation between the IFAC_TOT scores and RPFC region of the salience network. Pearson's r=-502.

Chapter 4:

DISCUSSION

Our findings suggest that patients with obesity were similar to controls in terms of cognitive functioning; however, they did significantly improve at 3 months post-surgery, especially at memory tasks. This improvement did not correlate with the improvement of HOMA-IR, CRP, and triglyceride levels. Correlating with weight loss after SG, patients' performance on cognitive tasks post-surgery could be related to the increased activity observed between the hippocampus and the precuneus cortex. In addition, patients with obesity had greater reward sensitivity as measured by PRT compared to controls, and this elevated state persisted even at 3 months post-surgery. Our results indicate altered FC within cognitive and reward-related connectivity at baseline in patients with obesity compared to controls.

In the self-report scales, none of the reports showed a significant difference between pre-surgery and post-surgery. "Perceived Stress Scale", anxiety and depression scores showed a decreasing trend at 3 months post-surgery, even though not reaching significance. Correlating with weight loss, depression and anxiety symptoms and stress-related factors observed commonly in obesity seem to be improving after SG surgery. Previous literature suggests improvement in the severity of depression symptoms even at 2 to 3 years after bariatric surgery and improvement in the severity of anxiety symptoms at 24 months post-surgery (Gill et al., 2019). Also, the perceived cognitive deficit evaluated by the Perceived Deficits Questionnaire (PDQ-5) is found to be associated with self-report measurements of anxiety, depression, and mental health-related quality of life in BS candidates at baseline assessments (Moscovici, Wnuk, Okrainec, Hawa, & Sockalingam, 2019). However, our study did not find any significant correlations of depression, anxiety and stress scales with the improved cognitive variables post-surgery. Current studies

on BS are also limited in evaluating depression and anxiety symptoms as they are not assessed as primary outcomes after surgery. Therefore, it is not possible to make a causal interference and further studies are needed to understand the role of mood disorder and stress factors in the BS process.

"Cognitive Failures Questionnaire," which questions different areas of cognition such as attention, memory, and perception, and "Barratt Impulsivity Scale", which assesses impulsivity, did not change at 3 months after SG surgery compared to pre-surgery. Both scales are self-report; therefore, they are perceived cognitive failures and impulsivity measures and might be limited in evaluating expected improvements in these areas.

There were no significant differences between patients with obesity and healthy controls in psychiatric symptomatology and stress reports scales. Although previous literature shows a significant link between obesity and psychiatric disorders such as mood and anxiety disorders. Our results can be due to the design of our experiment, as we only included patients with obesity with no previously diagnosed psychiatric disorders. Therefore, it was expected to see similar anxiety and depression levels between patients with obesity and controls.

In the Penn-CNP battery, tasks about visuospatial perception and memory, visual attention, and impulsivity significantly improved along with the "g" factor indicating overall task performance at 3 months post-surgery. This can be interpreted as an indication of cognitive improvement. Previous studies also point to rapid cognitive improvement until 24 months post-surgery, specifically in the memory, attention, and executive functioning domains of cognition (Spitznagel et al., 2015). Our findings reveal that this improvement can be as early as 3 months post-surgery.

In a recent study, people with obesity who performed just below average but did not have any diagnosis of cognitive impairments pre-surgery showed improvements in cognitive areas of attention, mental flexibility, inhibitory control, and processing speed at 6 months after RYGB (Meghelli et al.). There was a positive correlation between processing speed and body weight change following surgery. Similar to the Penn-CNP battery, this study applied a neuropsychological battery examining different aspects of cognition. Other studies also found increased attention and mental flexibility that persist up to 24-months post-surgery (Alosco, Galioto, et al., 2014). BS patients have better performance in memory assessed by "Verbal List-Learning Task" compared to controls with obesity after 12- weeks (49.21 ±10.78 vs. 44.24 ± 13.33; respectively) and 24-months (49.83 ±10.38 vs. 47.54 ± 10.70; respectively), and the improvements in memory correlate with lower BMI levels at 24-months post-surgery (Alosco, Galioto, et al., 2014). Assessed by a neurocognitive test battery (IntegNeuro), BS candidates who performed worse in cognitive performance at baseline compared to normal-weight controls, significantly improved in cognitive functioning at 2 weeks (by a 17% increase) and 14 weeks (by a 21% increase) post-surgery (Tucker et al., 2020). Together with these findings, we can suggest that the role of BS on cognitive function may be more substantial within the first months following surgery as the initial time period is when the most weight is lost, and other medical comorbidities improve that have a negative effect on cognition in people with obesity (Crémieux, Ledoux, Clerici, Cremieux, & Buessing, 2010). Resting-state fMRI studies also support our results; pre-surgery patients with obesity have decreased connectivity in the frontal areas such as OFC, superior and middle frontal gyrus, mPFC, gyrus rectus compared to healthy controls, and BS significantly recovered the disordered FC in these regions at 4 months post-surgery (Li, 2018). These findings suggest a possible role of BS in improving cognitive control and self-management.

It is important to note that even though the "Cognitive Failures Questionnaire" and "Barratt Impulsivity Scale" failed to change post-surgery, "Continuous Performance Task" as a measure of visual attention and impulsivity and the overall task performance to assess cognition did significantly improve. A study comparing self-report measures and neuropsychological test battery on cognitive functioning in BS candidates report no associations found between the subjective and objective results, indicating that BS candidates have little insight on their actual cognitive performance (Garcia et al., 2013). Therefore, contrary to self-report measurements, Penn-CNP neuropsychological battery is an objective, laboratory-based measurement and can therefore be a better indicator of cognitive improvement.

Unlike previous studies, there were no differences in any of the cognitive tasks in the Penn-CNP battery between patients with obesity and healthy controls. Most studies reported bariatric surgery candidates with cognitive deficits in attention, executive function, memory, and language domains pre-surgery (Alosco, Galioto, et al., 2014). Previous literature relates cognitive deficits in obesity to structural changes in the brain, such as smaller grey matter volume in the PFC, hypothalamus, cingulate gyrus, and hippocampus (Debette et al., 2011; Rullmann et al., 2018). Individuals with obesity also have abnormal glucose metabolism and reduced metabolic function, which might affect cognition (Volkow et al., 2009). Therefore, cognitive changes caused by obesity is considered to be a metabolic disease model affecting the brain. The inconsistency of our results with the literature can be a possible effect of our study's design. We only included individuals with obesity who were not depressed or anxious or had any current complaints about their cognitive abilities. Another reason we may have failed to observe a cognitive deficit in the baseline group with obesity could be that our sample was not extremely obese (mean BMI: 43.33 ±5.54 kg/m2). Most studies reporting cognitive dysfunction had a sample with a mean BMI of > 45.00 kg/m2. Greater BMI may have worsened

the metabolic dysfunction and brain abnormalities mentioned above in obese and led to a more significant cognitive deficit. Still, we believe this is a strength in our study; it was possible to eliminate baseline co-founding factors that may have an effect on cognition and relate the observed changes to obesity and disordered eating behaviors of patients with obesity, making a more causal interference.

A common explanation for cognitive improvement after SG surgery is the recovery of other medical conditions such as hypertension, type 2 diabetes along with metabolic functions such as insulin resistance and inflammation. In our study, we saw a significant improvement in biological markers on metabolic function (HOMA-IR, Hba1c, total cholesterol, triglycerides) and inflammation (CRP) at 3 months post-surgery. Research shows that BS improves insulin homeostasis and glucometabolic control assessed by HOMA-IR and Hba1c even in non-diabetic patients with obesity (Stenberg & Thorell, 2020). A study on glucose regulation and cognition shows that 12-months after RYGB, patients have better performance on memory, attention, psychomotor speed, and cognitive flexibility tasks along with improved HOMA-IR and Hba1c levels. Lower HOMA-IR levels successfully predict improvements in all cognitive domains mentioned (Galioto et al., 2015). The lipid profile also improves after SG when measured at 3-months and 12-months post-surgery (Milone et al., 2015) and is maintained for up to 4 years. The success of surgery measured by greater weight loss is associated with a more favorable lipid profile (Dixon & O'brien, 2002). Many researchers also focused on the relationship between inflammation and cognition in recent years as inflammation has been strongly linked to cognitive decline and dementia development. Inflammation is also observed during obesity; research on genetic mice models of obesity results in central inflammation (Miller & Spencer, 2014). Accumulation of white adipose tissue in obesity enhances inflammation and increases plasma levels of CRP, interleukins, IL1B and IL-6,

proinflammatory cytokines such as TNF-a, appetite-related peptides as leptin and resistin (Ouchi et al., 2011; Pohl et al., 2009). Even though in our study, we did not find any of these factors to be a significant predictor of improved Penn-CNP task scores, these markers can still be important in cognitive recovery observed after SG surgery. Further research is necessary that focuses on these relationships in a more complex framework.

Response bias measured by PRT was greater in patients with obesity than healthy controls, indicating greater reward sensitivities of patients with obesity. This finding supports our hypothesis that individuals with obesity have high response bias favoring the rich stimulus compared to controls. Based on previous neuroimaging research, patients with obesity have a hyperactive brain reward system, including NAc, amygdala, OFC, and anterior insula (Kenny, 2011). Patients with obesity also have increased resting-state FC between ventromedial PFC (vmPFC) and cognitive regulation regions such as dorsolateral PFC (dlPFC) and decreased connectivity between vmPFC and motivational areas such as ventral striatum (vSTR), indicating sensitive reward networks in obesity at rest (Schmidt et al., 2021). vmPFC and VSTR are both linked to the reward and valuation processes, in other words, reward sensitivity.

On the other hand, response bias and discriminability did not change significantly after 3 months of surgery. In addition, the difference in reward bias observed at baseline patients with obesity and controls was also present between 3 months post-surgery and baseline controls. These results suggest that BS patients had elevated reward sensitivity remaining even after 3 months of surgery. A significant positive correlation is reported between reward sensitivity assessed by the “Behavioral Inhibition Scale/ Behavioral Activation Scale” and fast food and sweet drink consumption in children. Therefore, children with high reward sensitivities may be more interested in high-calorie dense food, making them vulnerable to developing unhealthy

eating behaviors and obesity (De Decker et al., 2016). A longitudinal study on reward sensitivity found that increased "Insatiability for Reward," a fixation to a particular reward, scores positively correlated with body weight, BMI, and waist-to-hip ratio for all age groups including ages of 9, 15, 18, 25 and 33 (Katus et al., 2020). These results suggest an association between high reward sensitivity and obesity. It is important to note that they reported significance on the "reward fixation" component of reward sensitivity, and in our study, we found significance on the "response bias" component, indicating a need to investigate different domains of reward sensitivity and its relationship with obesity.

A review on reward suggests that BS results in decreased neuronal activation in the reward networks towards food, which leads to successful weight loss (Scholtz et al., 2015). For example, BS patients have significantly reduced reward value of sweet and fat tastes in a progressive ratio task when assessed 8 weeks after surgery (Miras et al., 2012). However, the decreased reward from food after surgery can lead to addiction problems such as drugs of abuse, alcohol, gambling, etc., to obtain the lost hedonic responses that are used to be coming from food (W. C. King et al., 2017). Addictive substances in addiction and palatable food in obesity activate the same reward pathways in the brain, and when the rewarding value of food decreases after surgery, patients turn to addictive substances to activate the reward circuit. Also, both obesity and addiction can be associated with neurocognitive abnormalities such as reward learning, decision-making, and executive function (Ivezaj et al., 2017). In a longitudinal study, 14% of BS patients are diagnosed with substance use disorders such as tobacco, sedative, alcohol, cannabis, and cocaine 2 years after surgery. Interestingly, %70 of patients developed this problem following surgery (Reslan et al., 2014). Drug use is also associated with suboptimal weight loss following surgery and poor surgical outcome.

It is important to note that reward sensitivity measured by PRT is independent of any pleasurable stimuli such as food; therefore, it is a reliable indicator that patients with obesity continue to have greater reward sensitivities after BS, which might result in cross-addiction problems.

In addition, it is worth mentioning that PRT is a measure of anhedonia, defined as "reduced ability to feel pleasure", that needs a longer time period to show significant reward changes compared to phasic reward responses such as cocaine abuse. As this is a longitudinal study with short-term assessments, it may not have been possible to see the reward-related changes occurring in the long-term, and 3 months post-surgery might not have been a long enough time period to observe significant alterations in the reward system. The self-report measure for anhedonia, "SHAPS", also did not change post-surgery, further supporting our hypothesis. Anhedonia is a core symptom of depression, and previous literature shows a significant association between anhedonia and impaired reward mechanisms. Therefore, research with longer assessment periods to examine the effect of BS on anhedonia may be beneficial to expand our knowledge on obesity, BS, and reward mechanisms.

OFC, an important region for the reward pathway, is involved in sensory integration, representation of the experienced and expected value of the reward, and decision making for reward-related behaviors. The OFC has also been implicated in food-related reward evaluation as research suggests that it builds representations for food via sensory processing (sight, smell, taste, texture) and links them with satiety signals to create reward values for food and control food intake (Rolls, 2007). For example, even cognitive factors such as taste-related words (delicious, rich) can change the activations in the OFC. When food is not present, the liking of sweet food changes the FC between OFC and other reward brain regions in the resting state,

indicating a role of the OFC in the hedonic and motivational aspects of reward (Rolls, 2021). In our study, we found increased connectivity between left OFC and left middle and inferior frontal gyrus post-surgery. The middle frontal gyrus is part of the PFC and, based on previous research, has a role in cognitive abilities and self-control during food choices (Chen, He, Han, Zhang, & Gao, 2018). Both OFC and PFC are important in food-related rewards, and they are implicated in cognitive control and the experience of subjective pleasantness (Kringelbach, 2005). In individuals with obesity, effective directional connectivity to assess causal influence is observed between the right OFC to left OFC, left middle frontal gyrus, and right inferior parietal lobule, which can indicate a top-down regulatory role of OFC for cognitive, visuospatial, and attention networks. Abnormal connectivity between these regions may be causing overeating in obesity when exposed to external food cues (P. Zhang et al., 2019). Men with obesity had decreased synchronicity in the OFC and medial PFC (mPFC) activity in the fasted state, which may mean less inhibitory control than lean men (B. Zhang et al., 2015). In a study, pre-surgery bariatric surgery patients show decreased resting-state FC in the OFC, superior frontal gyrus, and gyrus rectus than normal-weight controls. Correlating with weight loss, regions with decreased connectivity recovered to normal levels 4 months after surgery (P. Li et al., 2018). After BS, the regulatory role of OFC may have been increased on the frontal regions contributing to improvements in cognitive performance related to visuospatial perception and attention.

Previous research provides strong evidence on hypo-functioning in some brain areas important for the reward system in patients with obesity. In our results, we saw decreased connectivity in left OFC to left OFC, frontal pole in patients with obesity compared to healthy controls. Studies also show decreased brain activity in the OFC in obesity compared to lean in the satiated state (Kilpatrick et al., 2014). The frontal pole is essential for cognitive capabilities such as action

selection, specifically selecting and updating models of reward possibilities based on environmental factors (Kovach et al., 2012). Our findings support the hypothesis that OFC signaling may be abnormal in patients with obesity and fail to exhibit a top-down regulation on cognitive functioning and inhibitory control, leading to overeating and obesity.

In people with obesity, lower FC was observed between left and right putamen and left middle and superior frontal gyrus than controls. Individuals with obesity have decreased activity to food-related stimuli in the superior frontal gyrus, middle frontal gyrus, mPFC, and OFC. These areas are important for cognitive control and reward processing, and lower activity within and between these regions might indicate impairments in the reward system and cognition. One study reported subjects with obesity to have increased connectivity between the left middle frontal gyrus and right putamen while viewing food pictures (Tuulari et al., 2015). This study might be different from our results as it is task-based. Further studies with non-task-based paradigms are needed to make meaningful interpretations of our results.

We also reported increased FC between the left amygdala and left OFC post-surgery compared to pre-surgery. An addiction study reported that chronic heroin users had increased FC between the amygdala and the lateral OFC compared to controls. Abnormal lateral OFC activity is known to take part in the neural mechanisms of drug addiction by failing to inhibit excess drug intake and resist impulses and cravings leading to compulsive drug-seeking (Volkow et al., 2005). Amygdala is important for the acquisition, consolidation, and expression of learning of drug-related cues (Hyman, Malenka, & Nestler, 2006). Previous literature shows that obesity and drugs of abuse share similar pathways in terms of reward. For example, anti-diabetes drugs such as GLP-1 agonists which induce weight loss are also effective in treating problems with drugs misuse (Eren-Yazicioglu et al., 2020). GLP-1 agonists decrease reward-related

abnormalities in multiple drugs of abuse and animal models have shown that GLP-1 agonists result in reduced palatable food intake and substance abuse. Even though, in terms of reward, our findings do not agree with the addiction study; it is important to note that our subjective and objective reward measurements assessed anhedonia, and as mentioned previously, it needs a longer period of time to show significant changes compared to the phasic reward responses experienced in drugs of abuse. On the other hand, the amygdala is also important in memory and information retrieval to visual stimuli; increased connectivity between OFC and amygdala might have contributed to memory acquisition and consolidation regulation, leading to better performance in face memory tasks.

Compared to healthy controls, patients with obesity had decreased connectivity between the left amygdala and left superior parietal lobule/ lateral occipital cortex/ precuneus. The precuneus is important in the salience network and is involved in the representation of the self. The precuneus and amygdala are implicated in the perception of negative feelings, such as embarrassment and guilt (Bastin, Harrison, Davey, Moll, & Whittle, 2016) Reduced connectivity between these two regions in individuals with obesity should be investigated further as they may have a role in emotions related to body perception and embarrassment and guilt about eating behaviors. A resting-state fMRI study also found increased connectivity between the right amygdala and precuneus in patients with obesity compared to control (Olivo et al., 2017). Even though this is contrary to our results, the authors note that they were also expecting a connectivity change in the opposite direction.

We found increased connectivity between the left hippocampus, an important region for cognition, and the precuneus cortex post-surgery. The main functions of precuneus include memory recollection, episodic memory retrieval, mental imagery strategies, and integration of

information. A study on calorie restriction in women with obesity found that after 12-week low-calorie diet and having sustained weight loss over 4 more weeks, women with obesity perform better on a recognition memory task along with increased resting-state FC between the hippocampus and parietal areas, including left precuneus and left angular gyrus (Prehn et al., 2017). Previous research also found that older subjects reduced coherence in the activity among brain regions related to memory formation, such as precuneus, parietal cortex, and hippocampus (Grady, Grigg, & Ng, 2012). Bariatric surgery also leads to significant weight loss, especially in the first following months after surgery. Like changes seen with calorie restriction, post-surgery patients with obesity performed better on cognitive tasks in Penn-CNP battery, which may be linked with the increased activity observed between the hippocampus and the precuneus.

Compared to controls, people with obesity had increased connectivity between the right hippocampus and right putamen/ insular cortex, between the left hippocampus and right inferior frontal gyrus, and between the left hippocampus and putamen. A recent study reported decreased resting-state activity in the hippocampus and putamen in patients undergoing SG. These resting-state activities correlate with changes in BMI and craving for high-calorie foods after surgery (Gu et al., 2020). After surgery, the decreased resting-state activities of these regions may have resulted in weight loss and improvement in eating patterns as the hippocampus and putamen important roles in regulating overeating behaviors and obesity.

DMN includes regions that are active when subjects are awake and at rest without focusing on any specific task, and activity diminishes in these regions during specific-goal-directed behaviors. Altered resting-state FC in the DMN has been frequently associated with cognitive decline in memory formation and neurodegeneration (Buckner, Andrews-Hanna, & Schacter,

2008). In patients with obesity, greater FC was observed between the mPFC and the middle frontal gyrus than controls. mPFC has a vital role in decision making, including executive control and reward-guided learning. A study on children with obesity showed that obesity have higher connectivity between the middle frontal gyrus and the vmPFC (Black et al., 2014). Combined with our results, these findings indicate greater FC between reward and self-control pathways in people with obesity, making these individuals more vulnerable to external food-related stimuli such as high-fat junk foods or visual food cues.

There were no FC differences in the DMN between post-surgery and pre-surgery results of the patients with obesity. There were also no differences between significant areas of the reward network, such as NAc, putamen, ventromedial PFC, and the anterior insula post-surgery. These findings support our results on the reward learning task, PRT, as no differences were found on response bias between pre-surgery and 3 months post-surgery. One possible limitation of our study could be the second assessment time interval, as 3 months might not be sufficient to observe any reward-related changes. However, a recent study reported that BS does not significantly change resting-state FC of the reward network (NAc, putamen, amygdala, anterior insula) and the DMN compared to controls with obesity at 6 and 12 months after surgery (Heinrichs et al., 2021). Therefore, the unaltered reward pathways observed after BS can be an important contributor to the development of other addictions and regain of weight after surgery. Further studies are needed to widen our knowledge of the relationship.

Previous literature shows that obesity is consistently associated with hyper-connectivity increased FC within the salience network (Sturm, 2007). The salience network detects and filters salient stimuli and recruits relevant functional networks. It also has a role in food awareness (Kullmann et al., 2012). A resting-state fMRI study focusing on the salience network

reported increased intrinsic connectivity strength in the salience network of patients with obesity (García‐García et al., 2013). We found increased functional connectivity within three regions of the salience network in patients with obesity compared to controls: 1) between the right anterior insula and right middle temporal gyrus/ SMG 2) between right rostral PFC and left planum temporale/ SMG 3) between left SMG and left planum temporale/ parietal operculum. Garcia-Garcia concluded that in obesity, abnormal activation in the salience network might result in an imbalance between autonomic processing and rewarding effects of food, leading to overeating.

When the insula was assessed as a separate seed from the salience network, increased connectivity was observed between the right insular cortex and right OFC in patients with obesity compared to controls. Insula is associated with homeostatic regulation of hunger and plays a part in integrating food-related interoceptive signals (Voss et al., 2010). Dysfunctional insular cortex activation may disrupt satiety signaling, and when activated with reward-related regions as OFC, it may increase the rewarding value of food and enhance satisfaction from eating, therefore, contributing to obesity. In a recent review on resting-state fMRI, individuals with obesity show a consistent pattern of increased OFC and decreased insular cortex compared to healthy controls (Parsons, Steward, Clohesy, Almgren, & Duehlmeyer, 2021). Abnormal homeostatic signaling is a feature of obesity; increased FC between homeostatic and reward-related brain regions is observed in lean individuals but not in obesity (Wijngaarden et al., 2015). These results are contrary to our findings; more studies are needed to understand the relationship between these regions and obesity.

We found decreased connectivity between left SMG and left planum temporale/ superior temporal gyrus and between right rostral PFC and left superior parietal lobule post-surgery in

the salience network. The supramarginal gyrus (SMG) is part of the lateral parietal cortex, involved in bodily processing parts, salience detection, and self-regulation. As the temporoparietal network is essential in AD literature, there was an experiment on mild AD patients which reported that glucose metabolism correlated positively with Mini-Mental State Examination (MMSE), measuring dementia severity, within the parietal lobe, including SMG, and temporal lobe, including superior and middle temporal gyrus in a PET scan (Bokde et al., 2005). Therefore, these two regions may be necessary in cognitive function, and decreased connectivity seen in our findings can be associated with cognitive improvement observed 3 months after SG.

Even though anterior insula seed in the salience network did not significantly differ, the right insular cortex had decreased connectivity with the right middle temporal gyrus post-surgery. A study found decreased FC in the left insular cortex within the temporal lobe network in individuals with obesity/ overweight compared to healthy controls (Kullmann et al., 2012). The temporal lobe network includes the primary and secondary auditory cortices and the insular cortex. The insular cortex contains the primary gustatory cortex responsible for the perception of taste and flavor and is required for appropriate control of feeding behavior and food preferences (Oliveira-Maia et al., 2012). The temporal lobe network, including the insular cortex, is an appetite-stimulating circuit. Post-surgery, the decreased connectivity between these areas may act as an inhibitor to orexigenic behaviors such as overeating and contributing to weight loss after weight loss SG.

The dorsal attention network includes regions that are active during externally directed attentional tasks. The IPS is involved in sensorimotor integration, such as forming intentions and cognitive plans for specific types of movements. We found increased connectivity between

the right IPS and right postcentral gyrus in patients with obesity compared to controls. The postcentral gyrus is the primary somatosensory cortex and is part of the sensorimotor and visual networks. The close relation between the sensory cortex and cognitive networks such as attention has been investigated in obesity-related studies (P. Zhang et al., 2021). For example, food images, food intake, food-related cues result in increased activity in the right precentral and left postcentral gyrus (sensorimotor networks) in individuals with obesity compared to controls (Carnell, Gibson, Benson, Ochner, & Geliebter, 2012). A study on stroke patients found significantly higher functional connectivity between the primary motor cortex and the anterior IPS of the ipsilesional hemisphere in well-recovered stroke patients than healthy controls when evaluated 3 months after stroke (Schulz et al., 2016). They concluded that the posterior parietal cortex could be important for integrating signals from multiple sensory and motor areas to facilitate recovery after focal lesions such as stroke. Therefore, in obesity, IPS may act as a top-down modulator of the sensorimotor areas. The increased connectivity observed in patients with obesity can create a neurobehavioral vulnerability leading to abnormal eating behaviors when facing food-related visual stimuli.

Strengths and Limitations

The sample size of our fMRI data was limited to 19 SG patients with obesity with pre- and post-surgery results and 15 healthy controls. We could not have the fMRI data of all participants who have completed the computer tasks and self-report measures due to various reasons such as agoraphobia, implants, inability to fit into the 64-channel head coil, and having COVID-19 after surgery, and one participant had arachnoid cyst detected at the fMRI session. Even though our sample size is appropriate based on previous literature on the subject, we believe adding

more participants to the study would make the observed FC changes more prominent, and more accurate interpretations would be possible.

As another limitation, we did not include diet, lifestyle changes, and activity levels as covariates for our results. For example, including a questionnaire such as Yale Food Addiction Scale (YFAS) would be important to understand changes in attitude toward food, food addiction levels, and eating behaviors after surgery. A study shows that SG results in successful weight loss and decline in maladaptive eating patterns measured by YFAS. YFAS scores also correlate with reduced resting-state FC between the precuneus and the putamen (Dong, 2020). In our study, we included subjective and objective reward tasks independent of food stimuli. This may have been a limitation as the literature suggests the most common changes observed after BS are on food-related tasks and self-reports. In addition, after BS, patients become more active in their daily lives, and long-term weight loss maintenance after BS has been correlated with regular physical exercise (Martin-Fernandez, Creel, & Schuh, 2021). Therefore, exercise can be an important factor in our results as we saw significant FC changes in regions involved in sensorimotor control.

In our study, controls were only assessed at baseline, and there was no follow-up at 3 months. This can be a limitation as we could not eliminate the practice effect as a confounding variable. The patients with obesity completed the Penn-CNP battery and PRT task twice, 3 months apart; this may have improved performance. A test-retest reliability study on Penn-CNP found that practice effect is present in episodic memory and executive problem-solving tasks when applied 2 weeks apart (Izgi et al., 2021). The most significant practice effect is seen in memory-related tasks indicating memory to be more susceptible to changes related to practice. The time period between sessions, age, and gender of the subjects may affect the results (Calamia, Markon, &

Tranel, 2013), and some tests are known to be resistant to practice effect; in the Penn-CNP battery, research on these factors is limited. Therefore, comparing with other studies using Penn-CNP battery, we concluded the practice effect should not be as significant in our study due to the longer time interval (3 months) between each assessment as longer application periods are expected to minimize practice effects.

There are also several strengths of this study. We believe this experiment has many unique values and will significantly contribute to basic and clinical sciences. First, psychiatric features and cognitive characteristics observed in individuals with obesity who applied for BS in Turkey can be defined in a large sample.

Secondly, the relationship between obesity and cognitive symptoms is examined in terms of psychosocial and biological factors. We used a standardized and computational cognitive test battery that has not been used in previous studies, and functional images of the brain are obtained focusing on the cognitive networks. In this context, different aspects of obesity and cognition and their neuroanatomical and biochemical relationships are examined.

The relationship between obesity and the reward system is evaluated temporarily. This is one of the first studies to measure reward in obesity independent of food-related stimuli with a reliable, standardized reward learning task, “PRT”. We examined reward sensitivities of BS patients with healthy controls to develop a complete framework on the role of the reward system in BS. We believe our results have important implications in BS research, such as determining factors contributing to the process, insight into the neural mechanism of the reward system when combined with resting-state results, and identification of potential biomarkers.

This study investigates the course of BS as all measures were repeated at 3rd month after bariatric surgery. It was a longitudinal assessment investigating multi-dimensional domains that can affect the process of surgery. Also, the time interval between two assessments was relatively short; therefore, we could eliminate confounding factors such as complications observed commonly after surgery and more confidently relate the observed changes to obesity and disordered eating patterns to understand the predictors of surgery outcomes.

These findings can be helpful as guides for physicians in preliminary evaluations and follow-up of these patients. They can lead further research in the development of new therapeutics to increase success rates in bariatric surgery and reduce adverse outcomes, which can develop after surgery.

Future Perspectives

Research has suggested inflammation's role in the relationship between cognition and obesity. As mentioned previously, obesity leads to adipose tissue dysfunction and triggers the release of proinflammatory cytokines (TNF-a), appetite-related peptides (leptin, resistin), CRP, and interleukins (-IL1B, IL-6) (Ouchi et al., 2011; Pohl et al., 2009). IL-1B and IL-6 impair cognitive and memory-related neuronal networks (Gemma & Bickford, 2007), and elevated IL-6 might reduce processing speed and execution function (Trollor et al., 2012). Also, C-reactive protein and IL-6 are linked to an increased risk of dementia (Koyama et al., 2013). Elevated IL-1B, IL-6, TNF-a mRNA expression levels in the hippocampus, important for learning and memory, is also observed in metabolic syndrome model mice and mice fed with the HFD compared to control (Jeon et al., 2012). In mice, a HFD also accompanies enhanced microglial activation in the hippocampus; microglia act as regulators of inflammation through the release

of pro-inflammatory cytokines and chemokines (Loane & Byrnes, 2010). It is well known that IL-1B, IL-6, and TNF-a have roles in synaptic plasticity and LTP formation, which is important for learning and memory (Yirmiya & Goshen, 2011). Research shows that over-expression of IL-6 or exposure to elevated concentrations of TNF-a results in reduced LTP in hippocampal slices of mice (Bellinger, Madamba, Campbell, & Siggins, 1995; Cunningham, Murray, O'neill, Lynch, & O'connor, 1996) These results emphasize the critical effect of inflammatory markers on cognition, especially learning and memory. These biomarkers are essential moderators in cognitive and reward abnormalities commonly seen in obesity. Correlating with weight loss, after SG, we expect to see an improvement towards normalization of plasma levels of these inflammatory marks and appetite hormones and improved cognitive function. We believe adding these factors as covariates to our study design would help identify potential biomarkers in the BS process.

GLP-1R's are widely expressed in the brain. Previous research suggests that GLP plays a role in reward processing and neuroprotection. Recent studies have shown that the use of GLP agonists is neuroprotective, especially in disorders where cognitive impairment is accompanied, and neural degeneration is evident, such as AD and Parkinson's disease (Salcedo et al., 2012). In RYB surgery patients, an agent suppressing plasma GLP-1 levels correlated with palatable food reward in a progressive ratio task, food appeal scores, and increased activation of important reward regions such as NAc, caudate, anterior insula, and amygdala (Goldstone et al., 2016). The GLP-1 antagonist, Ex-9, induced reduced connectivity in the right middle frontal gyrus and right caudate nucleus at pre-RYGB and decreased connectivity in the right OFC post-RYGB (van Duinkerken et al., 2021). Ex-9 also more significantly increased the connectivity in the left lateral occipital cortex post-RYGB compared to pre- RYGB, and this correlated with a greater BMI change, savory food appetite scores, and hunger scores. Based on these findings,

we believe the dynamic changes in the serum GLP levels after BS might have an important role in the observed cognitive improvements in our study. Therefore, in addition to inflammatory markers and metabolic parameters, GLP-1 levels can be analyzed in relation to the post-surgery cognitive alterations.

Stress is a significant risk factor for obesity, and early negative life events may affect the outcome after bariatric surgery (Alciati, Gesuele, Rizzi, Sarzi-Puttini, & Foschi, 2011). In cases of childhood early negative life events, negative work-life events, traumatic life events, and a decreased sense of social support, people make more unhealthy dietary choices and are more likely to gain weight (Sockalingam et al., 2017). Research shows that chronic stress can cause stress-induced eating and may lead to weight gain and the development of obesity (Torres & Nowson, 2007). In addition, sleep patterns disrupted by stress, peripheral adipose tissue innervation, and glucocorticoids also contribute to obesity by affecting the metabolism and increasing eating. Again, these etiological factors may make them more impulsive, and they may have difficulty controlling their eating behavior and preventing food cravings (U. D. H. Y. Eser). The stress response is also an important factor for initiating and maintaining mood disorders, psychosis, and cognitive decline (Keller et al., 2017; Lara et al., 2013). One hypothesis is that stress causes overactivity of the hypothalamus-pituitary-adrenal gland (HPA) axis and increases cortisol levels. Cortisol is an important regulator of appetite hormones such as neuropeptide-Y and leptin. Chronic increase in cortisol may result in the accumulation of abdominal fat mass through these appetite hormones, increased nutrient uptake (Björntorp, 2001), and insulin resistance (van der Valk, Savas, & van Rossum, 2018). There are many unknowns about the effects of stress on metabolism and studies about stress factors in BS patients are lacking (Hensel, Kaplan, Anvari, & Taylor, 2016). More detailed research is needed

for the role of stress in obesity and how it may be affecting the course of BS since they are known to correlate with psychiatric comorbidities.

Obesity is associated with reduced brain volumes in grey and white matter (H. K. Karlsson et al., 2013). The reductions in the grey matter are more prominent in the cortical areas such as frontal, parietal, temporal areas, which are important for cognition. Research shows that obesity-induced structural brain changes can lead to cognitive dysfunction later in life (Walther, Birdsill, Glisky, & Ryan, 2010). Adipose tissue, elevated blood pressure, hyperglycemia, hyperlipidemia, inflammation may be mediators of the obesity-related loss of structural brain volume (Friedman, 2014; Karlsson, 2013). Interestingly, BS patients show increased grey matter volume after surgery, and these recoveries are mainly observed in occipital and inferior temporal regions (Tuulari et al., 2016). Research on the effect of BS in obesity-induced structural alterations is limited and existing literature is controversial. As a future direction, grey-matter changes (such as grey matter loss, cortex atrophy) that occur in the entire brain without focusing on a specific region can be evaluated. Afterward, ROI assessments can be performed on brain areas known to be associated with cognitive functions such as the PFC, hippocampus, and temporal lobe in post-surgery patients with obesity compared to their pre-surgery results.

In conclusion, SG may cause an improvement of cognition, especially in memory tasks, even as early as three months post-surgery; however, reward bias in patients remains unchanged. Our analysis shows that improvement of cognitive function may not correlate with the improvement of HOMA-IR, CRP, and triglyceride levels but may relate to FC changes in the brain. Other biomarkers as GLP-1 and inflammatory cytokines and stress-related factors might be mediating

this relationship, and it needs further assessment and evaluation of structural changes within the brain.

Chapter 5:

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